FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE DRUG AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM) AND THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE (AADPAC)

Tuesday, June 11, 2019

8:00 a.m. to 5:23 p.m.

Day 1

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. HERNANDEZ-DIAZ: Good morning. I would first like to remind everybody to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Lyndsay Meyer.

If you are present, please stand; back there in the room. Thank you.

My name is Sonia Hernandez-Diaz, and I will be chairing today's meeting. I will now call the Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee to order. We will start by going around the table and introducing ourselves. We will start with the FDA to my left and go around the table.

DR. STAFFA: Good morning. I'm Judy Staffa. I'm the associate director for public health

initiatives in the Office of Surveillance and Epidemiology.

DR. HERTZ: Sharon Hertz, director of the Division of Anesthesia, Analgesia, and Addiction Products in the Office of New Drugs.

DR. McAninch: Good morning. I'm Jana McAninch. I'm the senior medical officer on the prescription drug abuse teams in the Division of Epidemiology.

DR. EGGERS: Good morning. I'm Sara Eggers. I'm in the decision support and analysis team here in CDER.

DR. NELSON: Good morning. I'm Lewis Nelson. I'm the chair of emergency medicine and a medical toxicologist from Rutgers New Jersey Medical School in Newark, New Jersey, and I oversee the New Jersey Poison Center.

DR. KATZMAN: Hello. I'm Joanna Katzman. I'm a professor at the University of New Mexico and senior associate director at Project ECHO, University of New Mexico. Thank you.

DR. MIKOSZ: Good morning. I'm Christina

Mikosz. I'm a medical office through at the CDC in the Division of Unintentional Injury Prevention.

DR. ZIVIN: Good morning. Kara Zivin, professor of psychiatry, University of Michigan, research scientist, Department of Veterans Affairs.

DR. MARSHALL: Hi, everyone. I'm Brandon Marshall. I'm an associate professor in epidemiology at the Brown School of Public Health.

DR. HOFFER: Lee Hoffer. I'm an associate professor of medical anthropology and psychiatry at Case Western Reserve University in Cleveland, Ohio.

DR. LESAR: Good morning. Timothy Lesar, director of clinical pharmacy services and patient care services director, Albany, New York, Albany Medical Center.

DR. MEISEL: Good morning. Steve Meisel, director of medication safety for Fairview Health Services in Minneapolis.

DR. BOUDREAU: Good morning. Denise Boudreau. I'm a scientific investigator at Kaiser Permanente Washington and also a professor at the University of Washington, and I do

pharmacoepidemiology research.

DR. GRIFFIN: Good morning. Marie Griffin, professor of health policy and medicine at Vanderbilt University.

DR. CHOI: Moon Hee Choi, designated federal officer.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz, professor of pharmacoepidemiology at the Harvard Chan School of Public Health in Boston.

DR. LITMAN: Ron Litman. I'm a professor of anesthesiology in pediatrics at the University of Pennsylvania and Children's Hospital Philadelphia, and the medical director of the Institute for Safe Medication Practices.

DR. URMAN: Rich Urman, anesthesiologist, Brigham and Women's Hospital in Boston, Massachusetts.

DR. JOWZA: Hi. I'm Maryam Jowza. I'm an anesthesiologist and a pain physician at University of North Carolina at Chapel Hill.

DR. ZACHAROFF: Good morning. I'm Kevin Zacharoff, faculty and clinical instructor and

course director of pain and addiction at the State University of New York, Stony Brook School of Medicine.

DR. McAULIFFE: I'm Laura McAuliffe, professor and director of the nursing anesthesia program, East Carolina University, Greenville, North Carolina.

DR. McCANN: Hello. Mary Ellen McCann, an associate professor of anesthesia at Harvard Medical School and a pediatric anesthesiologist at Boston Children's Hospital.

DR. GOUDRA: Basavana Goudra, anesthesiologist at Penn Medicine, Philadelphia.

DR. GARCIA-BUNUEL: Good Morning. Martin Garcia-Bunuel. I'm a primary care physician and the deputy chief of staff at the VA Maryland Health Care System in Baltimore.

DR. MACKEY: Hi. Good morning. Sean Mackey, professor and chief of the Division of Pain Medicine at Stanford University.

DR. SHOBEN: Good morning. I'm Abby Shoben. I'm a biostatistician at the Ohio State University.

DR. HIGGINS: Jennifer Higgins, the AADPAC consumer representative.

MS. ROBOTTI: Suzanne Robotti, DSaRM consumer representative and executive director at DES Action and founder of MedShadow.

MR. O'BRIEN: I'm Joe O'Brien, president and CEO of the National Scoliosis Foundation. I am the patient representative. I am also a patient who has had six spinal fusion surgeries for my scoliosis. I'm fused from T4 to the pelvic.

DR. SCARAZZINI: Good morning. I'm Linda Scarazzini and the head of pharmacovigilance and patient safety at AbbVie and the industry representative on DSaRM.

DR. HUMMEL: Good morning. Michelle Hummel. I'm the pharmacologist at Otsuka Pharmaceutical in Princeton, New Jersey.

DR. HERNANDEZ-DIAZ: Thank you. We also have Dr. Terri Warholak joining us through the phone because of flight cancellations.

Would you like to introduce yourself, please?

DR. WARHOLAK: Good morning. My name is Terri Warholak, and I am a professor and assistant dean at the University of Arizona, College of Pharmacy.

DR. HERNANDEZ-DIAZ: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these

proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now I'll pass it to Moon Hee Choi, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration is convening today's joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representatives, all members and temporary voting members of these committees are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of these committees' compliance with federal ethics and conflict of interest laws, covered by but not

limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of

their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

For today's agenda, the FDA is seeking public input under clinical utility and safety concerns associated with the higher range of opioid analgesic dosing, both in terms of higher strength products and higher daily doses, in the outpatient setting. FDA is interested in better understanding current clinical use and situations that may warrant use of higher doses of opioid analgesics.

We are also interested in discussing the magnitude and frequency of harms associated with higher doses of opioid analgesics relative to lower doses, as well as optimal strategies for managing these risks while ensuring access to appropriate pain management for patients.

FDA frequently hears from patients and healthcare providers that higher dose opioid

analgesics continue to be a unique and necessary necessary part of effective pain management for some patients. FDA is also cognizant of serious safety concerns associated with both higher strength and higher daily doses of opioid analgesics both in patients and in others who may access these drugs.

Higher strength products may be more harmful in cases of accidental exposure and overdose, and may also be more sought out from misuse and abuse. Along with a number of other factors, a higher daily opioid dose is associated with greater risk of overdose.

Concerns have also been raised that higher dose opioid regimens may carry a higher risk of addiction, although robust evidence for a casual relationship is lacking. There is a strong association between higher opioid dose and duration or persistence of opioid analgesic therapy, and assessing temporal relationships and independent effects of opioid dose and duration on the risk of both addiction and overdose is challenging.

In addition, FDA acknowledges the complex and evolving landscape of the opioid epidemic, with myriad federal, state, local, and payer efforts to encourage more judicious prescribing of opioid analgesics and the growing threat of highly lethal illicit opioids.

To better understand both the clinical utility and harms of higher dose opioid analgesics in the current environment and to discuss the advantages and disadvantages of various potential risk management strategies, FDA brings these issues to an advisory committee to seek input and advice from the clinical, patient, public health, and research communities.

In particular, FDA seeks to discuss:

1) The current clinical use and situations that may warrant pain management with opioid analgesics at higher product strengths and daily doses, factors influencing prescribing practices, and specific patient populations for whom there may be utility in prescribing these medications at higher doses;

2) The magnitude and frequency of harms associated with opioid analgesics at higher product strengths and daily doses, relative to lower strength in daily doses, including the role of opioid dose in adverse health outcomes in both patients and in others who may access the drugs; for example, risk for developing addiction, fatal overdose, the relevance of therapy duration and physical opioid dependence, and risks in different subpopulations; for example, patients with chronic non-cancer pain, young children, adolescents; and

3) Possible FDA interventions and their expected impact on patients and public health more broadly, including, for example, potential effects on prescribing and pain management practices, patient experiences and behaviors, and adverse outcomes such as addiction and overdose.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest

waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Linda Scarazzini and Michele Hummel are participating in this meeting as nonvoting industry representatives, acting on behalf of regulated industry. Their role at this meeting is to represent industry in general and not any particular company. Drs. Scarazzini and Hummel are employed by AbbVie and Otsuka Pharmaceutical Development and Commercialization, respectively.

With regard to the FDA's guest speakers, the agency has determined that the information to be provided by these speakers is essential. The following interests are being made public to allow the audience to objectively evaluate any presentations and/or comments made by the speakers.

Dr. Sandra Comer has acknowledged consulting

fees from Charleston Labs; Collegium; Egalet; Epiodyne; KemPharm; Mallinckrodt; and Nektar.

Dr. Beth Darnall is a clinical professor at Stanford University and part-time chief science officer at AppliedVR. Dr. Darnall has acknowledged stock options in Axial Healthcare and compensation per annum for serving as the company's scientific advisor.

She has also acknowledged current involvement as investigator on several contracts and/or grants for the treatment of chronic pain and pain management, funded by the National Center for Complementary and Integrative Health and National Institute of Child Health and Human Development of the National Institutes of Health, and Patient-Centered Outcomes Research Institute.

In addition, Dr. Darnall has acknowledged receiving consulting fees from Stanford and elsewhere for conducting healthcare clinician certification training workshops.

Dr. John Markman has acknowledged advisory board membership and/or consulting fees from Clexio

Biosciences; Editas Medicine; Flexion Therapeutics; Tremeau Pharmaceuticals; Sophren Therapeutics; Greenwich Biosciences; Salix; Quark Pharmaceutical; Quartet Therapeutics; Collegium; Purdue; Biogen; Novartis; Aptinyx; Nektar; Plasmasurgical; Allergen; Pacira; Grunenthal; Eli Lilly; Depomed; Janssen; Teva; Kempharm; Abbott; Chromocell; Convergence; Inspirion; Pfizer; Sanofi; Daiichi Sankyo; and Trevena.

Dr. Michael Rowbotham has acknowledged being a past member of a scientific advisory board for Nektar related to their development of a new opioid product until May 2017.

Dr. Hilary Surratt has acknowledged receiving several contracts and/or grants from the National Institutes of Health; National Center for Advancing Translational Sciences; and Patient-Centered Outcome Research Institute to examine injection drug use in rural Kentucky; interventions for peripartum opioid-use disorder in rural Kentucky; and opioid overdose prevention in 16 counties across Kentucky.

Dr. Surratt is currently a principal investigator, or co-investigator, on seven studies, four with substance-use focus.

Dr. Bobbi Jo Yarborough has acknowledged being a co-principal investigator or site investigator on two ongoing FDA-mandated postmarketing studies of extended-release and long-acting opioid analgesics. These studies are funded by the Opioid Postmarketing Consortium, currently comprised of the following companies: Allergan; Assertio Pharmaceutics [sic], Incorporated; BioDelivery Sciences, Incorporated; Collegium Pharmaceuticals, Incorporated; Daiichi Sankyo; Egalet Corporation; Endo Pharmaceuticals, Incorporated; Hikma Pharmaceuticals USA, Incorporated; Janssen Pharmaceuticals, Incorporated; Pernix Therapeutics Holdings, Incorporated; Pfizer Incorporated; Purdue Pharma LP; and SpecGX, LLC.

Dr. Michael Von Korff has acknowledged being a co-investigator on study grants funded by the Patient-Centered Outcomes Research Institute,

concerning opioids and chronic pain. Dr. Von Korff has retired from Kaiser Permanente Washington Research Institute on May 1, 2019 and is serving part-time as advisor or co-investigator on research grants funded by Patient-Centered Outcomes Research Institute and National Institutes of Health to Kaiser Permanente Washington Research Institute and University of Washington.

Dr. Von Korff is also an unpaid board member of Physicians for Responsible Opioid Prescribing, a nonprofit organization.

As guest speakers, Drs. Cicero, Comer, Darnall, Goldberger, Markman, McPherson, Rowbotham, Surratt, Von Korff, Yarborough, Ms. Farrell, and Mr. Kiezulas will not participate in committees' deliberations, nor will they vote.

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and

their exclusion will be noted for the record.

FDA encourages all participants to advise the committees of any financial relationships that they may have regarding the topic that could be affected by the committees' discussions. Thank you.

DR. HERNANDEZ-DIAZ: We have three more members to introduce. Dr. Horn, Dr. Sprintz, and Dr. Becker, do you mind introducing yourself?

DR. HORN: Good morning. My name is Pamela Horn. I'm a clinical team leader in Division of Anesthesia, Analgesia, and Addiction Products.

DR. SPRINTZ: Hi. Michael Sprintz. I'm an assistant professor in Division of Geriatrics and Palliative Medicine at University of Texas Health Science Center. I'm boarded in anesthesia, pain medicine, and addiction medicine, and I've been in recovery myself from substance abuse for over 18 years. I run a private practice clinic that specializes in treating chronic pain and substance abuse in Texas. Thank you.

DR. BECKER: Good morning. Will Becker,

associate professor of internal medicine at Yale School of Medicine, and I direct a multidisciplinary pain clinic at VA Connecticut.

DR. HERNANDEZ-DIAZ: Thank you.

We will now proceed with the FDA's introductory remarks from Dr. Judy Staffa.

FDA Introductory Remarks - Judy Staffa

DR. STAFFA: Good morning. Dr. Hernandez-Diaz, members of the Drug Safety and Risk Management Advisory Committee, members of the Anesthetic and Analgesic Drug Products Advisory Committee, guest speakers, guests from the public who've come to this meeting in person, and those who are listening in via webcast, welcome to this two-day public advisory committee meeting, and thank you for your interest in this important issue.

As you've heard, over these next two days, we will discuss the clinical need for and safety concerns associated with high daily doses of opioid analgesics and the high dosage strength products often used to achieve these doses. This is a

complex topic on which many strong opinions are held, but our goal is to examine the data, both quantitative and qualitative, around both the clinical need and the potential harms.

We frequently hear from patients and healthcare providers through public meetings, such as our recent patient-focused drug development meeting on chronic pain, that higher dose opioid analgesic therapy and higher dosage strength products continue to be a unique and necessary part of effective pain management for some patients. However, we are also aware of increasing public concern about the risks these regimens and products pose to both patients and others in the community.

Some stakeholders have asked the agency to withdraw the approval of higher dosage strength oral and transmucosal opioid analgesics due to safety concerns. Higher dosage strength products may be more harmful in cases of accidental exposure and overdose and may also be more sought out for misuse and abuse.

Along with other important factors, a higher

daily opioid analgesic dose is associated with greater risk of overdose. Concerns have also been raised that higher dose opioid analgesic regimens may carry a higher risk of addiction, although robust evidence for a causal relationship is lacking.

In addition, we acknowledge the complex and evolving landscape of the opioid epidemic with many federal, state, local, and payer efforts to encourage more judicious prescribing of opioid analgesics and of course the growing threat of highly lethal, illicit opioids.

It is in this complex and changing environment that we need to consider potential regulatory actions that would impact the availability of higher dosage strength products to varying degrees depending on the action taken. As regulators, we know that taking any action requires careful consideration of the potential impacts of that action and the trade-offs between the desired positive impact and the potential negative impact on patients and the public health.

When considering regulatory strategies relating to opioid analgesics, FDA always considers two equally important fundamental public health goals. We want to ensure that products are available to meet the medical needs of people living with debilitating pain while reducing opioid misuse, abuse, addiction, overdose, and death. We also need to ensure that our actions are supported by the best available data.

Another important goal, therefore, is to strengthen our scientific understanding of the biological and behavioral drivers of misuse, abuse, and addiction, and the risk factors that increase the likelihood of overdose and death.

FDA is increasingly moving toward a decision analysis-based approach when assessing potential regulatory actions intended to address the opioid crisis. This means considering the decisions and behaviors of multiple stakeholders, including healthcare providers, patients, communities, insurers, and others. It also means fully evaluating the interrelated set of factors that can

affect opioid analgesic use and impact opioid misuse, abuse, addiction, overdose, and death.

Dr. Sara Eggers from our Office of Program and Strategic Analysis will provide a framework for systematically considering these interrelated factors. This can help set a context for discussing what we know and what we don't know about the impacts of potential actions, and she will also articulate a number of key uncertainties we have identified.

She will be followed by several FDA speakers describing the regulatory history of these products and describing what we know about the dispensing and clinical use of high daily doses of opioid analgesics and high dosage strength products based on our own analyses as well as the medical literature.

FDA speakers will also present data on the associated risks of addiction, abuse, and overdose based on our review of the published literature. We will additionally note some of the challenges of determining a threshold for defining high dosage

strength products and the gaps in data to support such cutoffs based on risk.

You will then hear from multiple guest speakers who will share their research, knowledge, and/or experience about the clinical utility and a variety of risks associated with high-dose opioid analgesics, including abuse liability and the development of opioid-use disorder, and what we know about their involvement in fatal drug overdose cases.

Later this afternoon, we will hear from clinician researchers about the experiences of two healthcare systems, the Veterans Health Administration and Kaiser Permanente in Washington State, when they instituted programs to reduce high daily doses of opioid analgesics for their patients, and we'll also hear about the challenges associated with opioid tapering.

Tomorrow morning, we will provide you with some examples of FDA's past and current regulatory actions to manage opioid-related risks so our discussion can focus on the impact of potential

additional actions that would target higher dose opioid analgesics.

We will then hear from the public who have taken the time to come to share their knowledge and experiences with the committees. Finally, we will spend tomorrow afternoon going through a number of discussion questions, which my colleague Dr. Sharon Hertz will walk us through.

You will note that we are not focusing our discussion on any specific regulatory action, and we are not asking the committees for a vote. Rather, we are looking for a robust discussion on the potential impacts of any action we might take to reduce prescribing and access to high daily doses or higher dosage strength products in this complex and dynamic environment.

Before we begin our discussion, I'd like to acknowledge the elephant in the room. We know that high-dose opioid analgesic therapy is very closely related to long duration of therapy or chronic use. The effectiveness or benefit of chronic opioid analgesic therapy, whether high dose or low dose,

is a closely related topic on which many strong differing opinions are also held.

The FDA has recently been given new authorities to require pharmaceutical companies to conduct postmarketing studies of effectiveness under the SUPPORT Act of October 2018. Be assured that although we will not be focusing on that topic today, FDA is working diligently to determine how best to use those new authorities to formally improve our understanding of the effectiveness of chronic opioid analgesic therapy.

So while this topic may certainly come up, we will focus our discussion for these two days on higher dose opioid analgesic therapy and higher dosage strength products, a topic which certainly merits its own discussion.

Our goal in having this public meeting is to gain insights from what folks outside of FDA have learned about the uncertainties we've identified. We can then use these insights to make informed decisions about potential regulatory actions to minimize unintended adverse consequences to

patients and their families and communities while maximizing public health benefit from optimal management of safety risks, including misuse, abuse, addiction, overdose, and death.

I thank you all in advance for taking the time to share your knowledge with us and to inform our decision-making. Thank you.

DR. HERNANDEZ-DIAZ: Thank you.

We will now proceed with the FDA presentation by Dr. Eggers.

FDA Presentation - Sara Eggers

DR. EGGERS: Good morning. I'm Sara Eggers with CDER's Decision Support and Analysis team, and I will follow up on Dr. Staffa's remarks by presenting a framework for systematically thinking through the issues and input that will be discussed at this meeting.

As Dr. Staffa has conveyed, opioids present a complex public health challenge. There is no simple solution. Strategies to address this challenge include regulatory actions by FDA within a context of actions taken by many public health

and regulatory stakeholders. Assessing those strategies requires understanding a complex system of behaviors and effects, all of which are hard to predict in isolation.

A system-focused framework can inform our understanding of the potential impacts of regulatory action. It can convey a complexity of all the moving parts. It can break down that complexity into factors that can be systematically considered, and it can sharpen focus on the factors that are subject to the greatest uncertainty.

In 2017, the National Academies of Science, Engineering, and Medicine recommended FDA consider such a framework. This is a novel approach. The goal is to set context for the wealth of input that will be brought forth over the next two days. It also may provide a useful structure for the advisory committees to consider the evidence and uncertainties. This framework is high level. I will touch upon terms and concepts that will be defined and discussed in more detail in subsequent FDA presentations.

There are three basic elements of the framework. First are the regulatory actions that FDA may consider. We will not outline the specifics of any potential regulatory action at this meeting. Instead, we will frame actions in terms of their intent and scope.

Next, are the ultimate outcomes to account for. These outcomes align with the two public health goals that Dr. Staffa outlined to reduce the negative impacts of opioids balanced with ensuring that treatments are available to meet patients' pain management needs.

Finally, to understand how actions may result in outcomes, we need to articulate the contributing factors, the many interrelated behaviors, the clinical aspects of opioids' pain and addiction, and importantly, the current context or environment of opioid use. I'm now going to walk through each of these elements in more detail.

There are many actions that FDA can take to manage risks associated with higher dose opioids and impacts will vary depending on the actions

taken. Again, we will not get into specifics, but an important feature is the intent of the action.

It is important to note the actions FDA is already taking to manage the benefits and risks of opioid analgesics. Dr. Horn will provide more detail on these actions tomorrow. But there are additional actions to consider, and it is important to separate out whether those actions are intended to reduce or target prescribing of higher daily dose, or of higher dosage strength products, or to improve the safety of products in some other way.

With intent in mind, another important aspect is the scope. Generally speaking, actions can range from less restrictive to more restrictive, as shown by the sample of actions. Again, Dr. Horn will outline this in more detail tomorrow.

Next, we define the public health outcomes. We first consider that impacts are not the same for all individuals. There are individuals who require treatment for pain, and we'll use the shorthand patient. There are individuals who misuse or abuse

opioid analgesics, and there are individuals at risk of accidental exposure. Note that a person can move from one situation to another or fit more than one at the same time.

Opioids can lead to negative outcomes for all individuals, and the intent of any regulatory action is to reduce these harms. We make a distinction in this framework. One is the outcome of overdose, including death, that is not associated with opioid-use disorder; for example, by children or adolescents who are experimenting. Two is addiction and opioid-use disorder and all of the associated harms, including overdose and death. Dr. Hu will define and discuss these effects in more detail.

In line with our goals, we must consider how actions may negatively affect patients in other ways, including inadequate pain management, impacts of stigma and treatment burden, and other associated harms such as withdrawal symptoms of tapering or suicide.

The most complicated task is outlined in the

links between actions and outcomes and the contributing factors. I will now present a graphical model called an influence diagram showing the factors in their relationships. Please note that only the factors identified as being most relevant to today's meeting discussion are shown.

I will walk through this model in stages. First I'll focus on potential impacts to patients and then to others exposed to opioids. A quick primer on the model: shapes denote a factor; outcomes are hexagon; and contributing factors are ovals. An arrow means that one factor is believed to be associated with another factor. Note the relationship suggested by an arrow may not be causal.

First, let's focus on the patients. The model starts at the left with FDA's potential regulatory actions, which I outlined earlier. The model ends at the right with the outcomes I also outlined.

To get from the actions to outcomes, we first consider the influence of FDA's actions on

prescribing practices. This includes healthcare providers' decisions about the products, strengths, and doses they prescribe, along with a number of other things they decide. For simplicity, we include here decisions by others in the healthcare system such as insurers. The degree of change in prescribing practice may vary depending on the type and scope of regulatory action.

In order to understand any potential changes, we must understand the current and evolving landscape of opioid use. This includes understanding the current rates of prescribing and in what clinical situations, as well as other current influences on prescribing practices. Corinne Woods and Pamela Horn will speak more to this context.

Prescribing affects patients' use of products in terms of the dose, strength, number of pills, et cetera. Patients' use is associated with risk of overdose and the development of OUD. For example, a patient's overdose risk may decrease due to lower dose exposure. On the other hand,

medication errors resulting from a change in a patient's regimen could increase risk.

There are a number of other clinical factors that must also be considered, including dose and dosage strength, duration of use, and individuals' risk factors such as age, tolerance, and comorbidities. All of these factors have to be taken into account.

We also consider the potential for undertreated pain. This may be tempered by the use and effect of other treatments for pain. Undertreated pain leads to concerns about the potential increase in misuse or abuse of prescription opioids or transition to illicit substances such as heroin, both of which increase the risk of overdose and development of OUD.

Finally, we include other patient harms, which I outlined earlier, resulting from undertreated pain or from challenges navigating the healthcare system, including stigma and treatment burden.

I'm going to clear this screen for a moment,

and we'll focus on other individuals exposed to opioids. We still have FDA's actions on the left, and on the right the negative impacts of opioids, overdose and death not associated with OUD, and development of OUD and associated harms.

Prescribing practices are relevant here, too, as is the potential for diversion; for example, due to leaks in the supply chain or illegal prescribing. Again, understanding the potential changes requires considering what is currently happening in the landscape.

Changes in prescribing and diversion can lead to changes in the volume of prescription pills in the community, which is a factor that represents the accessibility or exposure of prescription opioids to individuals. When discussing volume, we consider changes in the volume of higher strength products, and FDA's actions could result in decreases here. We also consider the volume of lower strength products, which very much depends on how prescribing practices may change based on any action. I'll speak more to this in a few minutes.

The volume or accessibility of pills can influence the risk of unintended exposure; for example, by children. It could also influence intentional misuse or abuse of prescription opioids. We are including the transition to illicit drug use; for example, resulting in changes of supply. The outcomes of any of these types of opioid exposures depend of course on the same clinical factors we outlined earlier: dose, strength, duration, and risk factors.

For reference, here are both submodels pulled together into one full model showing the focus on patients at the bottom and the focus on other individuals at the top. As a reminder, although complicated, this is still a high level depiction of complex issues intended to help account for and focus on the factors most relevant to actions relating to higher daily dose and dosage strength products.

Even so, the committees may identify missing factors relevant to daily dose or dosage strength that may have a significant influence on patient in

public health.

As FDA considered this issue, a number of key uncertainties emerged, and I will walk through those now using the model. The first is uncertainty about potential changes in prescribing practices due to any specific regulatory action; that is, how often and in what situations prescribers compensate by prescribing more lower strength pills, taper patients, add concomitant medications, and refuse to continue caring for some patients.

As you saw in the model, prescribing behavior is a key factor that links to almost every other factor. Therefore, uncertainty here leads to uncertainty about almost everything else.

Second is uncertainty about the incremental risk of harm associated with dose and dosage strength; in particular, the relationship between dose and dosage strength on the development of addiction and OUD. Rose Radin and a number of other guest speakers will speak more to this uncertainty.

Third is uncertainty about how regulatory actions may ultimately affect patterns of misuse, abuse, and transition to illicit drug use by patients and by others. This is particularly important given the increasing prevalence and lethality of illicit drugs.

Finally is uncertainty about how changes in prescribing in the healthcare system more generally may lead to other unintended patient harms. Currently, we see anecdotal reports of forced tapering or discontinuation leading to severe withdrawal, as well as increases in stigma. We lack data on the scope of these problems.

With the systematic accounting of the uncertainties, our goal with this framework is to build toward a summary assessment of the potential public health outcomes of various actions under consideration.

Here's an illustration showing the types of actions along the left and key effects in ultimate public health outcomes along the top. It's important to note that one should expect outcomes

to change even if FDA does not take on additional actions because the landscape of opioid use continues to change.

The question is what additional impact, positive and negative, would result from actions intended to reduce or target the prescribing of higher dosage strength or higher daily dose? A structure like this lets us compare the predicted outcomes and articulate the dependencies and uncertainties. The committees may find this a helpful way to organize their thinking.

In summary, taking any regulatory action to manage the benefits and risks of opioid analgesics requires careful consideration of the complex opioid system and the potential for intended and unintended consequences.

There are significant uncertainties about the impacts of potential actions, particularly about the behaviors of prescribers, patients, and others, as well as uncertainties about the risk of harm attributable to higher daily dose and dosage strength products.

FDA and guest speakers, public commenters, and committee members will all provide input on these issues. Varying perspectives about these uncertainties can lead to different opinions about what may be the best course of action. Therefore, we hope that a system-focused framework outlined here can help build a shared understanding and foster effective deliberation of the evidence and perspectives.

I would like to thank Blake Bannister for help in preparing this presentation, and thank you for your time.

DR. HERNANDEZ-DIAZ: Thank you, Dr. Eggers.

We will now proceed with the FDA presentation by Dr. Hu.

FDA Presentation - Ning Hu

DR. HU: Good morning. My name is Ning Hu. I'm a medical officer in the Division of Anesthesia, Analgesia, and Addiction Products. I'm also a practicing physician. Today, I will be providing an overview of regulatory background for opioid analgesics.

Here is the overview of the topics I'll be covering today. First, I'll touch base on the benefit and risk considerations when we make regulatory decisions for opioid analgesics. Then I'll discuss specific definitions related to opioid use and the dosage and treatment duration considerations associated with opioid use. I'll then explain some important prescribing information in opioid labeling, and I'll end with a brief discussion regarding morphine milligram equivalent, which is commonly used but debatable opioid dosage conversion tool.

The benefit-risk assessment is the foundation for FDA's regulatory review of human drugs and biologics. Given the unique features of opioid analgesics, including tolerance, physical dependence, addiction, misuse and abuse, we incorporate additional considerations in an extended benefit-risk framework for any decisions made involving opioid analgesics.

In the complexity of opioid crisis, all of our decisions are made with careful consideration

of potential impacts of that action and the trade-offs between the desired positive impact and a the negative impacts on patients and public health. The analgesic benefit of opioid is supported by numerous clinical trials and real-world evidence.

Despite the well-known adverse events and the risks to public health, opioids continue to be a necessary part of effective pain management when alternative treatment options are inadequate.

When we conduct risk assessment of opioid products, not only do we consider the risks to patients when the product is used as prescribed, such as the risk of serious respiratory depression; we also consider the risks when the drug was abused and misused.

Additionally, we consider the product risks that extend beyond individual patients to a broader public health such as the risk of abuse, misuse, addiction, and overdose that can be fatal. We also consider the safety of excipients for our products that may be taken for abuse by unintended routes of

administration. The risks are described in the product labeling, which is continuously updated when use of the information raise a concern.

It is important to recognize that tolerance and physical dependence are normal physiological responses to exposure to opioid. Tolerance is the need for increasing doses of opioids to maintain a defined analgesic effect of the drug in the absence of disease progression.

Physical dependence is a physiological state in which abrupt discontinuation or a significant dosage reduction results in opioid withdrawal syndrome. It is important to consider the facts of tolerance and physical dependence. When evaluating each patient using opioid analgesics for pain management, tolerance and physical dependence are separate and distinct from opioid addiction.

Opioid addiction is a chronic disease categorized by compulsive drug use despite adverse consequences. Opioid-use disorder is a related disorder defined according to a specific clinical diagnostic criteria.

Prescription drug abuse is defined as the intentional, non-therapeutic use of a prescription drug, even once, for its rewarding psychological and physiological effect. The occurrence of tolerance and dependence to opioids is not the same as addiction and can develop in the absence of abuse and addiction. Conversely, addiction abuse of an opioid are not always accompanied by concurrence of tolerance and dependence.

Given the features of opioid analgesics, it is challenging to develop and implement a single uniform approach when using opioid analgesics in the management of pain for all patients. Rather, patients should undergo individualized assessment of the benefits and risks for the specific circumstances and unique needs for each patient.

The big challenge is that individuals have wide variability in opioid tolerance and require a range of doses to obtain adequate analgesia and to minimize adverse reactions. Unlike other approved analgesic products, most opioids have no maximum daily dose based on the active ingredients because

there's no ceiling effect.

A few opioids have a maximum daily dose based on the maximum safe dose of a non-opioid component in combination of opioid and non-opioid products, or a product's specific dose-response relationship for toxicity for the specific opioid moiety. Further, no particular dose or treatment duration of any opioid has been determined to be a cutoff point between safe for use or unsafe for use.

The higher the dose, the greater the analgesic effect. It is also true that the higher the dose, the greater the risk for serious adverse events. Concerns have been raised that higher doses and longer duration of therapy may carry a higher risk to overdose, addiction, abuse, and misuse. However, a higher daily dose of opioids generally occur in the setting of longer duration of use, and there are limited data to distinguish between dose and duration and play a larger role in the risk for addiction, abuse, and misuse.

The opioid analgesic benefit has been long

recognized since the 19th century. In the early years, opioid analgesic products only marketed an approved immediate-release product and had been used primarily for acute pain and cancer pain.

In May 1987, FDA approved MS Contin, a morphine sulfate tablet. This is the first extended-release opioid that allowed dosing every 12 hours instead of every 4 to 6 hours. Corresponding to this dosing regimen, MS Contin extended-release tablet contains higher dosage strength of opioids.

Followed by approval of two other extended-release formulations -- Duragesic, a fentanyl transdermal patch in 1990, and OxyContin, an oxycodone extended-release tablet in 1985, higher dose strength opioids had been increasingly used in chronic pain management, and OxyContin had soon become a focal point of opioid abuse and misuse issues.

FDA has approved a variety of extended-release, long-acting and immediate-release opioid analgesics and a combination of opioid and

non-opioid products for outpatient use. A summary of extended-release, long-acting opioid products is shown in table 1, and immediate-release products in table 2 in the background document. It is important to understand the prescribing information for each product to ensure safe and effective use for that product.

The indication for extended-release, long-acting opioid analgesic is for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

The indication for immediate-release opioid analgesics is management of pain severe enough and for which alternative treatment options are inadequate. The indications are worded this way to alert the prescriber that opioids provide an analgesic option when alternative treatment options are inadequate, and all aspects of risks should be considered for the context of use with each prescription written.

A group of transmucosal immediate-release fentanyl products, also known as TIRF products, are only indicated for management of breakthrough pain in cancer patients who already tolerant to around-the-clock opioid therapy.

Opioid conversion information in product labeling is to enable the clinician to safely convert a patient from an existing opioid regimen to another with the consideration of incomplete cross-tolerance among different opioid products. It is a 1-week conversion and not safe to use conversely. The conversion factors neither describe equal analgesia nor suggest that the doses will have the same adverse reactions or euphoric effect.

Tolerance requirement described in the labeling represents that the conservative approach is recommended to ensure safe use of opioid. There are two aspects related to these requirements. When we initiate opioid therapy, we recommend that lowest initial those should be used for opioid-naive patients. Higher dose strength and

higher daily are only for use in opioid-tolerant patients.

Opioid tolerance is defined pragmatically. Based on the clinical trials experience, the clinician may individually titrate the drug to a dose that provides adequate analgesia and minimizes adverse reactions.

On the other hand, some opioid products given a the higher potency in dosage strength are only indicated for use in opioid-tolerant patients. The product includes Duragesic, a fentanyl transdermal product; Exalgo, the extended-release, hydromorphone tablet product; and a group of TIRF products as has been mentioned previously.

Finally, I'd like to bring back the topics of our discussion today, the clinical utility and safety concerns associated with the higher range of opioid analgesic dosing in terms of higher dose strength products and higher daily doses in the outpatient setting.

With all that has been said, we understand that it is challenging to define a cutoff value for

higher dosage strength or higher daily dose for safe and effective use. The morphine milligram equivalent, defined as an opioid dosage equivalency to morphine, is a commonly used opioid dosage conversion tool in pain management practice. However, based on our research and different resources and references, MME conversion is variable and conflicting, and there is no clear consensus for the context of use.

FDA has set up a working group to better define the extent of the variability to avoid miscalculations associated with harms, and the work is still in progress. However, a threshold of 90 MME has been frequently used to define higher dose daily doses for practical purposes.

The following FDA speaker, Corinne Woods, will get to this topic in detail. This concludes my presentation today. Thank you for your attention.

DR. HERNANDEZ-DIAZ: Thank you, Dr. Hu.

We will now proceed with another FDA presentation by Dr. Woods.

FDA Presentation - Corinne Woods

DR. WOODS: Good morning. My name is Corinne Woods, and I am a drug utilization team lead in the Office of surveillance and Epidemiology. Today I will present dispensing patterns in clinical use of higher dose opioid analgesics in the U.S.

In this presentation, I will first discuss defining higher dose opioid analgesics, presenting various definitions, as well as a brief discussion of morphine milligram equivalent conversion factors. Then I will present the results for dispensing patterns of higher dose opioid analgesics. This includes FDA analysis of nationally estimated data as well as reviews of published literature.

Lastly, I will present results for the clinical use of higher dose opioid analgesics as reported by selected healthcare systems from FDA analyses of Sentinel data and in published literature.

In the first section, I will discuss

defining higher dose opioid analgesics. There is no standard definition of higher dose opioid analgesics. This presentation includes results from FDA analyses, as well as reviews of published studies, and higher dose opioid analgesics were intentionally identified using various definitions for an expansive view on the complex and fluctuating prescription opioid analgesic market.

For each section, I will identify which definition was used to include products with at least 90 MME per unit, such as per tablet; products with at least 90 MME per day based upon the minimum labeled frequency; and prescriptions or patient's total therapy above a certain MME per day based upon pharmacy claims.

FDA analyses identified higher dosage strength products using the first two definitions, while the published studies we reviewed used the third definition to identify prescriptions or patients. For FDA analyses, we selected an arbitrary threshold of 90 MME. We acknowledge that CDC guidelines for prescribing opioids, which

identify a threshold of 90 MME per day, are well known and have been incorporated into numerous areas of practice. And some reimbursement policies use a 90 MME per day cutoff for action.

As mentioned in Dr. Hu's presentation, the FDA analyses used published conversion factors to calculate morphine milligram equivalents for each opioid products route per form and strength. We used a number of clinical resources for conversion factors, some of which are listed here. For methadone prescriptions, we used an MME conversion factor of 3, although this differs across daily doses. FDA analyses were conducted with the understanding that the field of MME research is ongoing.

In the second section, I will present results for dispensing patterns of higher dosage strength and higher daily dose opioid analgesics. For this section, we used the following data sources. For FDA analyses of national estimates of dispensed prescriptions, we used IQVIA's National Prescription Audit and press Total Patient Tracker.

We also reviewed published literature of dispensed prescription data.

I will now present results from the FDA analyses of national estimates of dispensed prescriptions. These analyses provide national estimates for opioid analgesic use in the U.S., and might provide a general context and possible scope for the potential impact of various regulatory actions that FDA may take, as Dr. Eggers discussed earlier and Dr. Horn will discuss further tomorrow.

In these analyses, we defined higher dosage strength products as oral and transmucosal opioid analgesics, where 1 unit, such as 1 tablet, contains 90 or more MME, and lower dosage strength products were less than 90 MME per unit. Our analyses also included all strengths of transdermal opioid analgesic products as a comparator. Some examples of higher dosage strength products in these analyses include oxycodone extended release 60 milligram tablet and fentanyl 800 microgram buccal lozenge.

We evaluated national estimates of opioid

analgesic prescriptions dispensed from U.S. outpatient pharmacies from 2013 to 2018. The Y-axis is the number of dispensed prescriptions in millions. The bottom gray bars are the number of prescriptions for lower dosage strength products, while the red bars are higher dosage strength products, and the white bars on top are transdermal opioid analgesics. This figure has a slight correction to the backgrounder.

Prescriptions for all strengths of oral transmucosal and transdermal opioid analgesics decreased 32 percent from 252 million prescriptions in 2013 to 172 million prescriptions in 2018. Prescriptions for higher dosage strength products comprised 1 percent or less of this market, and prescriptions for transdermal opioid analgesics comprised 2 percent.

The next slide shows this data in table format for a better look at annual prescription numbers. This table illustrates the steeper decline seen in prescriptions for higher dosage strength products compared to the other drug

categories. Between 2013 and 2018, prescriptions for higher dosage strength products, again in red, decreased 63 percent, while prescriptions for lower dosage strength products decreased 31 percent, and prescriptions for transdermal products decreased 34 percent.

These figures show the number of patients who are dispensed at least 1 oral transmucosal or transdermal opioid analgesic in 2018 from U.S. outpatient pharmacies in the U.S. An estimated 0.1 million patients received higher dosage strength products, again shown in red, while 52 million patients received lower dosage strength products, and point 0.6 million patients received transdermal opioid analgesics.

In addition to evaluating the number of dispensed prescriptions, we also evaluated the number of dispensed units, primarily tablets. This figure shows the number of oral and transmucosal opioid analgesic units dispensed from U.S. outpatient pharmacies from 2016 to 2018, during which time we saw a decline in dispensed units

across all MME categories examined. Over 85 percent of total dispensed units contained less than 20 MME per unit, and less than 1 percent of total dispensed units contained 90 or more MME, among which the largest proportions where those containing 90 up to 125 MME per unit.

Now, I will present results from published literature describing dispensing patterns of higher daily dose opioid analgesic therapy. First, I would like to discuss calculating daily dose from pharmacy claims. Here is an example of a prescription for hydrocodone/acetaminophen, 1 to 2 tablets every 4 to 6 hours as needed; dispensed 30.

Many pharmacies would enter the prescription day supply as if the patient would take the maximum, which would be 3 days. Some pharmacies may enter as if the patient takes the minimum around the clock, which would be 7 days, and in reality, the patient may take it only as needed.

Many researchers would calculate daily dose from this prescription as strength times the number

of tablets divided by day supply, then convert to MME per day. In doing so, they may overestimate or perhaps underestimate the actual daily dose taken by the patient, especially from drugs that patient takes only as needed.

With this in mind, we reviewed a study which examined national and state patterns in opioid analgesic prescriptions with a daily dose of 90 or more MME per day dispensed from retail pharmacies from 2006 to 2017. For these analyses, the daily dose was calculated using weighted day supplies that were manually inputted by pharmacies.

The analyses found a decline in the rate of higher daily dose opioid analgesic prescriptions between 2006 and 2017 per 100 U.S. residents. The prescription rates declined in every state during this period, the study period, and the variation between state prescription rates also declined. The same research team also saw a decline in higher dose opioid analgesic prescriptions as a percent of all opioid analgesic prescriptions from approximately 16 percent in 2006 to 14 percent in

2010, and declining down to 8.5 percent in 2017.

In the third section, I will present results in the clinical use of higher daily dose opioid analgesics. To evaluate the rationale for clinical uses of and restrictions on higher dose opioid analgesics, we sought qualitative information from selected healthcare delivery and payer organizations.

To evaluate utilization patterns and patient characteristics, we used the Sentinel Distributed Database, referred to here as Sentinel, which is a large robust sample of patients with public or commercial health care insurance. We also reviewed published studies of patients treated with higher daily dose opioid analgesics.

Now, I will present the data for selected health systems regarding the clinical needs for and restrictions on higher dose opioid analgesic prescribing. To collect qualitative information on these topics, FDA sent questionnaires to representatives from Selected Health Systems, listed here, as part of their existing research

contracts with FDA.

We asked them to provide expert input regarding the perceived clinical need for and restrictions on higher dose strength opioid analgesics, defined as oral and transmucosal opioid analgesics, which are more than 90 MME per day when 1 unit, such as 1 tablet, is taken around the clock at the minimum labeled frequency.

In describing the perceived clinical needs of these products, all health systems identified them as needed to treat pain in patients with cancer, terminal illness in need of palliative or hospice care, or more rarely, complex chronic conditions. Other considerations were that these products enabled a lower pill burden for some patients, an important factor with cancer or end-of-life care. They can also help keep prescriptions within reimbursement limits based upon pill quantity.

When asked what restrictions have been imposed on prescribing, all respondents indicated that states, payers, or both have placed limits on

the prescribing of higher dosage strength opioid analgesics. Some restrictions mentioned were prior authorizations needed before the insurer will reimburse the claim; pill quantity per prescription or per month; daily dose in MME; day supply; and extended-release products being covered only after immediate-release products were tried.

I will now present results from the FDA analyses using Sentinel data. For these analyses, we defined higher dosage strength products as oral or transmucosal opioid analgesics for which one unit, such as a tablet, taken around the clock at the minimum labeled frequency is 90 or more MME, and lower dosage strength products were less than 90 MME per day. Some examples of higher dosage strength products were oxycodone immediate release, 15 milligrams every 6 hours and oxycodone extended release 30 milligrams twice daily.

Between 2012 and 2016, patients with a higher dosage strength opioid analgesic claim, shown in red, comprised approximately 4 percent of all patients with an oral transmucosal or

transdermal opioid analgesic claim, and decreased 15 percent from 9.5 to 8 patients per 1000 Sentinel patients.

Patients with a lower dosage strength product claim decreased 12 percent from 219 to 193 patients per 1000 Sentinel patients. Patients with a transdermal opioid analgesic claim decreased 21 percent from 6 to 4.8 patients per 1000 Sentinel patients, and some patients were included in more than one analgesic category.

Sentinel results for the 5 years of data shown here included a large sample of Medicare patients, so patients age 65 or older may have been overrepresented in some of these analyses, and this figure does not include 2017 or 2018 results due to this data trend break.

For a look at patient demographics, from 2012 to 2018, our analyses included 1.8 million patients who had 27 million claims for higher dosage strength products; 47 million patients who had 351 million claims for lower dosage strength products; and 1.3 million patients who had 14

million claims for transdermal opioid analgesic products. Again, some patients represented more than one category.

The mean age of patients at the time of the prescription claim ranged from 57 years to 67 years old and the majority of claims were for patients aged at least 50 years old. However, again, this age distribution may have been influenced by the large Medicare sample included in the Sentinel analyses.

We evaluated clinical characteristics among a subset of patients with enrollment prior to starting an oral transmucosal or transdermal opioid analgesic product. Among the 1 million patients who started therapy with a higher dosage strength product during our study period, 66 percent of patients had claims with diagnoses codes related to back pain; 66 percent had claims for other nervous system conditions, which included a wide variety of diagnoses such as chronic pain syndrome, chronic pain due to trauma, and neuropathies; 61 percent had claims for arthritis and joint conditions; and

30 percent had claims for cancer.

Among the 35 million patients who started a lower dosage strength product, 37 percent had claims for arthritis and joint conditions; 30 percent had claims for back pain; 22 percent had claims for other nervous system conditions; and 17 percent had claims for cancer. Pain-related diagnoses for patients starting transdermal therapy were similar to those for patients starting therapy with a higher dosage strength product.

Of note, in this data source, a prescription claim is not linked to a diagnosis, so we were not able to assess indications. Instead, we looked for claims with selected pain-related diagnosis codes in the 6 months prior to opioid analgesic therapy start and the one month after. Patients had claims with more than one diagnosis of interest, and our analyses was not able to determine which exact medical condition the opioid analgesic was intended to treat.

We also evaluated comorbidity and the presence of claims with diagnoses related to mental

health conditions or substance-use disorder. Similar to assessing pain-related diagnoses, these were diagnoses of interest occurring in the 6 months prior to opioid analgesic therapy start or the one month after. We also calculated the Charlson-Elixhauser comorbidity score modified for a 6-month lookback instead of one year, and this is a slight correction to the backgrounder.

Patients who started a higher dosage strength product during the study period had a mean comorbidity score of 3.2, while those starting a lower dosage strength product had a mean score of 0.9, and those starting a transdermal opioid analgesic had a mean score of 3.8.

Fifty-four percent of patients who started a higher dosage strength product had a claim with a diagnosis associated with mental health and 9 percent had a claim for substance-use disorder. These proportions were higher compared to patients starting a lower dosage strength product and similar to patients starting a transdermal opioid analgesic.

For each opioid analgesic category, we also evaluated patients' cumulative length of therapy over the entire study period. Among patients who started therapy with a higher dosage strength product during the study period, the left column, 39 percent were on therapy with any higher dosage strength product for more than 90 days; 16 percent on therapy for 31 to 90 days; and 45 percent were on therapy for 30 days or less.

Among patients who started a lower dosage strength product, the middle column, 11 percent were on therapy with any lower dosage strength product for over 90 days and 76 percent of patients were on therapy for 30 days or less. Results for patients who started transdermal therapy were similar to patients who started higher dosage strength therapy.

Lastly, we reviewed published studies which evaluated patients who received higher daily doses based upon prescription claim data. We found two published studies which described the clinical characteristics of patients on higher daily dose

opioid analgesics, a VA study and a Kaiser Permanente study, both of which focused on longer term therapy for chronic non-cancer pain. These studies might not be broadly generalizable to current clinical use patterns, as the results are from 10 years ago from healthcare systems located on the west coast.

In the VA study, the patient characteristics were heavily influenced by the characteristics of all VA constituents. Out of approximately 14,000 VA patients with chronic non-cancer pain and at least one opioid analgesics fill, 3 percent were on higher daily dose therapy.

The Kaiser Permanente study was a volunteer cohort of approximately 2,000 patients with long-term opioid analgesic use of whom a weighted estimate of 16 percent of patients were on higher daily dose therapy. Here they define higher daily dose therapy of at least 90 days. The table shows the cutoff values that the research used to identify the higher daily dose per day, as well as patient's sex and age characteristics.

The clinical characteristics of patients with chronic non-cancer pain on at least 90 days of higher daily dose therapy were broadly consistent between the two studies. Compared to patients on lower daily doses, they were more likely to have multiple pain conditions and more comorbidities. They had a higher average pain score and substance abuse history was more common. However, the studies did not examine the timing of these outcomes with respect to starting higher dose therapy.

In conclusion, higher dose opioid analgesics have comprised a small portion of all opioid analgesic use. Prescriptions for higher dose opioid analgesics have decreased in recent years faster than lower dose and transdermal opioid analgesic prescriptions. Most opioid analgesic units dispensed, primarily tablets, contained less than 20 MME per unit.

Compared to patients on lower dose opioid analgesics, patients on higher dose opioid analgesics had multiple pain conditions; had higher

comorbidity; were more likely to have mental health conditions, including substance abuse; had longer durations of therapy with higher dose opioid analgesics; and appeared clinically similar to patients on transdermal opioid analgesic therapy.

Selected Healthcare Systems reported that higher dose opioid analgesics may be used to treat patients with a variety of conditions, including cancer and terminal illness. They also allow for lower pill burden for some patients needing higher dose therapy. This concludes the presentation for dispensing patterns and clinical use of higher dose opioid analgesics in the U.S.

DR. HERNANDEZ-DIAZ: Thank you, Dr. Woods.

We will now proceed with the last FDA presentation by Dr. Radin.

FDA Presentation - Rose Radin

DR. RADIN: My name is Rose Radin, and I will present FDA's review of epidemiologic studies of the associations between higher dose opioid analgesics and the risks of abuse, addiction, and overdose. The purpose of the review was to use

population health data to examine the extent to which higher prescribed doses of opioid analgesics contribute to the risks of abuse, addiction, and overdose. You'll recall from Dr. Eggers' presentation that these associations are relevant to assessing impacts from potential regulatory actions.

I will briefly present the literature review methods, share the results and discussion of studies for overdose and abuse and addiction, and then the conclusions of our review.

We used search terms to find relevant articles that had been entered in the PubMed online database for the past 10 years. We included studies that met basic design criteria, observational studies of risks in a population. Opioid analgesic dose was defined at a time point before the observed outcome, so in practice, the studies employed a retrospective cohort or case control design. The studies focused on patients with non-cancer pain in whom the considerations of safety and clinical needs may differ from cancer

pain. A few studies included patients with cancer pain as a minority of the study population.

As previous presenters have mentioned, there is no standard definition for higher opioid analgesic dose. What we found in our literature review was that no articles examined product dosage strength. All these studies examined average daily dose, and below is a general formula to give you an idea of what goes into average daily dose. Daily dose was agnostic of product dosage strength, and the studies defined higher daily dose in various ways.

On to studies of opioid analgesic daily dose and risk of overdose. Twenty-one studies of patients prescribed opioid analgesics met our basic design criteria. For data sources, the most common were electronic health record and claims linked to cause-of-death data. Other studies used EHR and claims, and some used pharmacy dispensing data linked to cause-of-death data.

Definition of daily dose was mainly categorical. One study analyzed daily dose as a

continuous variable. Study populations were generally comprised of prevalent users of opioid analgesics. Examples of populations included U.S. veterans treated at the VA health system and patients enrolled in a state Medicaid program. For adjustment for confounders, most studies adjusted for multiple demographic and medical factors; a few studies did not.

The studies consistently found that higher opioid analgesic daily dose was associated with higher risks of unintentional and intentional opioid overdose after adjusting for medical and psychiatric conditions and concomitant medications. Relative to 1 to 19 MME per day, which was commonly used as the reference category, there was an increasing risk of overdose deaths found with each increasing category of daily dose, with no threshold found that discriminates well between patients who will versus who will not go on to have an overdose.

Here are several estimates of the relative risk of opioid overdose in the 100 MME per day or

more category versus 1 to 19 MME per day. The X-axis shows the study that reported the relative risk and the study's definition of overdose. The Y-axis is the relative risk. Each dot is the relative risk of overdose from one study, and the whiskers show the 95 percent confidence interval. The relative risk estimates ranged from about 2 to about 9 based on the study definition of overdose and the population studied.

There are other interesting findings that are important to mention. Many prescription opioid overdoses occurred among patients on lower daily doses or with no prescription on record. For example, in one VA study, 67 percent of decedents with a current opioid analgesic prescription were on 90 MME per day or less.

In another VA study, 34 percent of decedents had no opioid analgesic prescription on record, and there are other examples from other populations. Also, studies identified several other strong risk factors: age 45 to 54 years; substance-use disorder history; mental illness; benzodiazepine

prescription; and skeletal muscle relaxant prescription.

We found studies with sufficient rigor that we believe the found positive association between higher daily dose of opioid analgesics and overdose. However, a precise and accurate magnitude of association is less clear because of numerous methodological challenges, including defining and measuring exposure, defining and measuring outcome, adjusting for confounders, assessing interaction, and applying the results to other populations.

I want to focus on key limitations that make it difficult to quantify the contribution of dose with confidence. One is residual confounding even after adjusting for confounders in the analysis because data on important confounders are incomplete in healthcare data. These important confounders include abuse and addiction, which also mediate the relation of daily dose to overdose, and psychosocial conditions such as family history of substance abuse and history of trauma.

These important risk factors may be contributing to the increased risk among patients on higher doses of opioid analgesics, and it's unclear how much. Also, the timing of exposure and outcome measurement matters when estimating the contribution of higher daily doses to overdose risk because while overdose is an acute event, in some cases there are numerous medical effects and behaviors that make up the path from prescription to overdose, which may take months or years to accumulate.

Most studies used prevalent users of opioid analgesics, but they did not examine the trajectory of daily dose from success of prescriptions. Evidence is just emerging on this issue, and recently, a study was published that found greater variability in the trajectory of daily dose was associated with a higher risk of overdose.

On to studies of opioid analgesic daily dose and risks of abuse and addiction. Abuse and addiction are harder outcomes to study than overdose, and this may explain why there is a

smaller body of literature on this question.

Three claims-based retrospective cohort studies met our basic design criteria. These studies differed in many fundamental design elements: definition of higher daily dose, which was alternately defined using increments of 10 MME per day or using a cutoff defined by the investigators; the definition of the outcome is all studies used a composite outcome defined by ICD-9 claims codes, but some studies included prescription opioid overdose in this composite outcome while one did not; the population studied and the criteria for prior exposure to opioid analgesics, which may affect their baseline risk of abuse and addiction; and adjustment for confounders, as some studies adjusted for medical and demographic factors as well as factors such as days supply or chronic use, while one did not make adjustment.

All three studies found some association, but is this association causal? In addition to the methodological challenges mentioned for studies of

overdose, these studies are also vulnerable to two major problems that preclude making a causal inference, reverse causation and ascertainment bias.

People with abuse that has been diagnosed and an insurance claim made are shown by the dark blue circle. They are excluded from the study. However, people with abuse or addiction that is undiagnosed or has not generated an insurance claim are shown by the gray circle. They remain in the study and they may escalate their daily dose at a faster rate than people without abuse or addiction. Therefore, it is uncertain whether the onset of abuse and addiction leads to higher daily dose or whether higher daily dose leads to the onset of abuse and addiction.

Patients on higher daily doses may have more opportunity to be diagnosed with opioid abuse and addiction; for example, if higher daily dose triggers risk screening or these patients have more or more severe comorbidities and are seen more frequently or for longer.

On to the conclusions. For higher opioid analgesic daily dose and risk of overdose, epidemiologic evidence suggests that higher prescribed daily dose contributes to increased risk of unintentional and also intentional opioid overdose. No threshold value was found that discriminates well between patients who will versus will not go on to have an overdose, and dose is one of multiple important factors influencing risk. A substantial proportion of prescription opioid overdoses occur in patients prescribed lower daily doses or with no opioid analgesic prescription on record.

For higher opioid analgesic daily dose and risks of abuse and addiction, limited data from retrospective health care claims-based studies suggest higher daily doses are associated with abuse and addiction, but it is uncertain whether higher daily dose plays a causal role in the development of abuse and addiction.

This is one of the key uncertainties Dr. Eggers mentioned when she presented the

framework for assessing impacts of strategies to manage risks. There's uncertainty because claims data likely capture abuse and addiction long after onset, if at all, leaving these studies vulnerable to reverse causation and ascertainment bias. Prospective studies and data from other disciplines may help answer this question. Thank you.

Clarifying Questions

DR. HERNANDEZ-DIAZ: Thank you, Dr. Radin.

Are there any clarifying questions for FDA? If so, please remember to state your name for the record before you speak, and if you can please direct the questions to a specific presenter.

Dr. Meisel?

DR. MEISEL: Steve Meisel. Very quick questions for Dr. Woods, please. In the IQVIA database, data that you presented, how did they define a dosing unit for liquid?

DR. WOODS: Hi. This is Corinne Woods. That's a very good question. One milliliter was defined as 1 unit for anything that was liquid.

DR. MEISEL: Even the highly concentrated

ones, where the intended dose is maybe a tenth of mL?

DR. WOODS: Yes.

DR. MEISEL: Okay. So then a related question with that, it's uncommon for high doses to be compounded in a compounding pharmacy. How was that, if at all, accounted for in that database?

DR. WOODS: We did not include those products in our analyses. We included oral, transmucosal, and transdermal products. If something is compounded, it's typically sold as a bulk powder, and we did not include those products.

DR. MEISEL: So it's possible the utilization is actually higher than what you presented because that was outside the scope of the database.

DR. WOODS: I cannot speak to that.

DR. MEISEL: And can I assume that that -- the database is prescription, so that excludes hospitals, and other institutions, and the VA. Is that correct?

DR. WOODS: These were prescriptions from

U.S. outpatient retail pharmacies.

DR. MEISEL: Right. So VA would be excluded.

DR. WOODS: Yes.

DR. MEISEL: Okay. Thank you.

DR. WOODS: Thank you.

DR. HERNANDEZ-DIAZ: Dr. Higgins?

DR. HIGGINS: This is also a question for Dr. Woods, and this may be conjecture. I'm just wondering if you found any explanations for reasons for the decrease in the higher dosage strength. I'm wondering if perhaps there is any evidence that there are increasing alternative products that are meeting the needs of patients.

DR. WOODS: Well, you're wondering if the patients who are using the higher dose products might have used alternative products. We didn't really analyze that. We just looked at the numbers of prescriptions and the number of patients. So we can't -- we don't know if they switched to a product or switched from a product. We did not analyze that. That's a good question, though.

DR. HERNANDEZ-DIAZ: Dr. Goudra?

DR. GOUDRA: Hey. Basavana Goudra Penn Medicine. Has anybody looked at the genetic predisposition? Have there been any family clusters? Are there enough studies to analyze that data?

DR. STAFFA: This is Judy Staffa. In our work, we've not been able to look at that.

DR. HERNANDEZ-DIAZ: Dr. Mackey?

DR. MACKEY: Yes, for Dr. Woods, two questions please; well, one a comment, the other question a question. On the decline seen with the higher dose strengths, when you do the math, in 2018, it looks like we're down to about 0.5 percent in that higher dose category. One, do you agree with that?

DR. WOODS: Yes, it was 0.5 percent. It was less than 1 percent.

DR. MACKEY: And two, you used a conversion factor of 3 for methadone, and we all recognize that methadone's a tricky drug and that it doesn't have a stationary potency, if you will. How do you

think that played a role in subsequent calculations, and was that same factor used in all the other studies that were mentioned as well?

DR. WOODS: That's a good question. I can't say what the studies used. I can only guess and I probably shouldn't. For our analyses, we did not have daily dose information for prescriptions, so we don't know if a patient is on 20 milligrams a day, 80 milligrams a day, and 5 milligrams a day. Unfortunately, we are restricted to the data that we have, so we used a factor of 3.

I can tell you that the majority of prescriptions were not products with methadone. They were hydrocodone, oxycodone, and morphine. Methadone is fairly small in the opioid analgesic market. I can't say whether a higher conversion factor might make a difference. I can only guess, and I would think not.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Shoben?

DR. SHOBEN: This is also for Dr. Woods, related to slide 28. Two questions. Actually, one is there's pretty clear evidence that the patients

receiving the higher dose strength products are sort of meeting multiple of these conditions for their prescription. One, did you look at any particular combinations that might be more common in the higher dosage strength product than the lower dose strength product? My second question is did you look at how these might have changed over time?

DR. WOODS: We didn't look over time. We did many analyses. Unfortunately, we couldn't do everything. In addition, we were limited by time, preparing for the AC.

Your first question was did we look at combinations? We did not. We just looked at one patient. We looked 6 months prior to the start of whatever each column was, and then one month after in case they saw the doctor.

Data is data. Claims sometimes show the diagnosis a little bit after they start, so that's why we looked at that period. During that period, they could have had a claim for back pain and a claim for arthritis. We didn't look to see what

they had together. That would probably take a long time to do that kind of research, so we don't have -- we have the capabilities for that but not the time.

DR. HERNANDEZ-DIAZ: Dr. Boudreau?

DR. BOUDREAU: Denise Boudreau. This is also a question for Dr. Woods. In your analyses, you focused -- and I understand why -- on 90 morphine equivalents or higher. I'm wondering if you did any analyses looking at other cutpoints such as the 50 to 90. I ask that in that when we taper patients, it's not uncommon that we try and get them below 50 or even below 30. So I'm wondering about the decline, or potential decline, in that group.

DR. WOODS: Can you pull up slide 13, please? That's a good question, and we did anticipate this question because we know there's a lot of different ways that you can look at data. Wouldn't that be great if we had a sensitivity analyses looking at various cutpoints?

When we look at the number of units, these

are units -- this is MME per unit, not MME based upon the lowest -- the label dose. When we look at this, you see that almost all of the units are well below 90; 50 would have been a good cutpoint, but we had to pick an arbitrary threshold, and we did pick 90.

If we did have the time and the capacity to do multiple analyses, we could have done 50, 120, and some of the other studies are even up to 300 MMEs per day, and this is what we were able to do and able to present and prepare for the AC.

DR. HERNANDEZ-DIAZ: Thank you.

Dr. Zacharoff?

DR. ZACHAROFF: Thank you. Kevin Zacharoff, and this is a question for Dr. Radin. In your conclusions, you stated that epidemiologic evidence suggests that higher prescribed daily dose contributes to increased risk of unintentional and also intentional opioid overdoses. I'm assuming that means opioid overdoses from prescription pain medications or from both?

DR. RADIN: Yes.

DR. ZACHAROFF: So not including illicit substances.

DR. RADIN: Yes, that's right.

DR. ZACHAROFF: Okay. Thank you.

DR. HERNANDEZ-DIAZ: Dr. Sprintz?

DR. SPRINTZ: Hi. Dr. Michael Sprintz. Actually, this is another question for Dr. Radin. One of the questions that I had is, when you guys were looking at the different factors, did you ever look at alcohol use, or diagnosis of alcohol abuse, or any other substance-use disorders other than opioids? Or was everything specifically geared just to looking back to only opioids almost in a vacuum?

DR. RADIN: Many of the studies that we reviewed adjusted for signs of substance-use history. These are studies that used EHR data, where they may be able to find an indicator for substance-use history. In fact, as I recall, there were a few studies that measured an indicator for alcohol use, an alcohol use disorder.

So they adjusted for these in their

multivariable model, and opioid dose was still a strong independent risk factor for overdose after this adjustment.

DR. SPRINTZ: I was actually worried more about the addiction risk as opposed to the overdose risk. Those are two different things.

DR. RADIN: Yes. Okay. Thanks for clarifying. The studies, they excluded people who had a prior claim for any kind of substance-use disorder. As I think many on the committee are aware, that's not a complete way of measuring, identifying people who have alcohol-use disorder or problems with substance use. But that's what the studies did to exclude people who might have prevalent substance-use problems.

DR. HERNANDEZ-DIAZ: Dr. Becker?

DR. BECKER: Will Becker. I think this is a question for Dr. Hu. You made a brief statement about the well-known effectiveness of opioids for various conditions. In light of, I believe it was, Dr. Woods' data showing that the most common

condition is chronic low back pain for which the high doses are prescribed, could you comment about effectiveness of opioids for chronic back pain?

DR. HERTZ: Hi. This is Sharon Hertz. I'm going to take that question. Low back pain is always a challenging condition to discuss in the context of opioids because we frequently hear that opioids don't work in low back pain, but in fact it's a clinical model that's sometimes used in analgesic development to look at efficacy. So we actually do have clinical trials, placebo control with rescue, our typical chronic pain study design, and it seems that they do work.

I think what we sometimes confound is whether or not they work versus whether or not they should be used, and if used, when in the management of low back pain they should be incorporated. So I think that there is evidence it works, but that's not the same thing as saying it should be like first-line therapy or anything like that.

DR. HERNANDEZ-DIAZ: Thank you. If there are no more questions --

DR. STAFFA: This is Judy Staffa. Can I just clarify, one of Dr. Meisel's questions was about whether VA data are included in the outpatient pharmacy. I just want to be clear that the answer of no, they're not is correct, but that means prescriptions dispensed by VA clinics or pharmacies would not be captured. But if a VA patient took a prescription to a drug store, such as a CVS or a Walgreens, that would be included.

So it's just not an exact answer. I just want to make sure that's clear.

DR. HERNANDEZ-DIAZ: Thank you very much.

We will now take a 15-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break among yourselves or with any member of the audience. We will resume at 10:00 a.m.

(Whereupon, at 9:45 a.m., a recess was taken.)

DR. HERNANDEZ-DIAZ: Welcome back. We will now begin with invited guest speaker presentations with Dr. John Markman.

Guest Speaker Presentation - John Markman

DR. MARKMAN: Good morning. My name is John Markman. I'm a professor of neurology and neurosurgery in Western New York. I want to thank the team at the FDA, Dr. Hertz and Dr. Staffa, for organizing this important meeting. I'd also like to thank my colleagues who are on these committees. Obviously, this is many of the leading minds, and the decisions and the recommendations that you make over the next couple of days are going to influence patients that we take care of. So as a colleague, as a citizen, and as a future patient, I just want to say thanks for your time.

I'm going to be talking from the perspective of a clinician. I've worked in a multidisciplinary pain center in an academic setting for the last 20 years. I'm really going to focus on this issue of dose and how the context in which you take care of a patient creates a lot of dilemmas.

The purpose of this meeting is to characterize the specific clinical use of these higher product strengths and daily doses of

opioids. I think the best way I know how to characterize the clinical use is to bring you into the exam room. So I'm going to do that today through video with patients I've seen over the last few months.

I think we can really just illustrate a lot of what we've heard in these fantastic presentations from Dr. Woods, Dr. Eggers, and just kind of bring those perhaps to life through the voice of the patient. Then we're going to try and identify specific populations for whom there may be clear benefits. Clear may be a tall order from what we've seen in the earlier slides today and from what you're about to hear.

My relevant experience for this, in addition to seeing patients just about every day and thinking about these issues deeply, is a meeting that took place in this room about 11 years ago. I came here because I was concerned about this very issue, but in a slightly different context.

The two committees that you're on were contemplating a decision about whether to extend

the indication for rapid-acting fentanyl formulations to chronic non-cancer pain, specifically to low back pain syndromes, which were the study populations.

As a clinician, I was deeply concerned about this because I felt that, potentially, making this wider indication for rapid-acting fentanyl formulations to chronic low back pain and chronic non-cancer pain syndromes in general would jeopardize the benefit-risk ratio for opioids in general; and that the patients who were most likely to benefit from these would not get them, and the patients who were most likely to be harmed would.

So it was in the very context that we're discussing this 11 years, hence, when I first came here because this editorial that I wrote was included in the briefing packet. I actually spoke at that podium over there as someone who had applied to speak for seven minutes as a member of the open public hearing. That's how my time on these committees began, thinking about these very same issues and, again, trying to find this balance

of how do we preserve and create guard rails around a therapy which we know is effective for some people but also endangers many others, and how do we make it as safe as possible.

So this talk has four components. I'm going to speak about need. I'm going to speak variability and individualized response, titration, and then a few little points about trade-offs at the end. I'll start with need. As I said, the best way to illustrate this is through hearing it from patients.

These cases all have something in common. As you've heard this morning from some of the presentations, neck and low back pain are the leading indications for analgesics, the leading indication for patients to come into subspecialty pain care, and a leading indication for even primary care treatment of chronic pain. So I'm going to focus on cases that, at least begin as their point of departure, have an element of chronic neck and low back pain.

These are all non-cancer pain syndromes

because I think that's really where the debate is, and these are all dilemmas. For most people who are in pain medicine, I think, as a daily focus of their work -- at least in my own case, I spent the first part of the 2000s, to about 2010, trying to wean patients off high-dose opioids most of the time.

That was the focus of my opioid practice. We had a buprenorphine detox, and we tried to take patients who we thought were unsafe doses and were not performing well in their daily activities and their lives, and tried to bring them down off opioids. In the last five years, I've had this role reversal, as there's been a collapse in opioid prescribing. I tend to have to actually prescribe more opioids now because of the patients like the one you'll see.

I'm going to start with this gentleman, Sam. He's 56. He's a gentleman with chronic low back pain.

(Video played and transcribed.)

"What's the most serious medical problem you

have right now?

"Right now would be my back pain and subsequent back pain, sciatic pain, and the muscle spasms that they create."

DR. MARKMAN: This is a gentleman who's had prior back surgeries. As you can see, looking at a sagittal CT image here, this is a CT myelogram. He's had previous back surgery. I actually saw him for back surgery many years ago. But he's here now, and he has intractable pain because of what's circled at the top of your screen, which is a collapse of the endplate at T12.

So he's had a compression fracture for about 9 months. This is a 56-year-old gentleman with a 9-month history of axial predominant low back pain, but with some radiation into the leg. And here's his story in a little more detail, and a little bit more about the comorbid conditions you heard about in some of those earlier talks this morning.

(Video played and transcribed.)

"Your original cancer was?

"Acute myeloid leukemia diagnosed on May 8th

of 2013.

"And you had a bone marrow transplant?

"I had a stem cell transplant on August 27th of 2013.

"And that pushed you to remission?

"It did temporarily. It came back. I had to go back on chemo, and it went away on May of 2014 and has been in remission ever since.

"For the past 5 years?

"Yes.

"Terrific.

"Yeah."

DR. MARKMAN: So he not only has chronic low back pain. He also has this prior history of treatment for his leukemia.

(Video played and transcribed.)

"My cancer's been in remission for 5 years this month.

"And when were you first diagnosed with graft-versus-host disease?

"August of 2013.

"Has that been painful?

"Yes. It's been -- it was very painful, and this has helped with that substantially.

"Because you were not on Exalgo at that time when you were first diagnosed.

"No, I was not. I was not. And that has helped dramatically with the muscles spasms that I get from that disease. They're just -- they're undescribable. When you get them in your rib cage, I mean, you can't run that out. It's underneath your rib cage or in your rib cage. My wife would tell you that if she just touches it, it would send me through the roof.

"What's the worst part of being on the Exalgo, or dilaudid, or hydromorphone, as it's called?

"I don't have any bad thoughts about it. I'm able to keep my mind clear. I'm not slurring my words. I feel -- my head feels normal, which is really nice.

"You seem a little short of breath right now. What's that from?

"The shortness of breath is from the

graft-versus-host."

DR. MARKMAN: The clinicians in the room, when we think about risk, I think there's a lot of focus on opioid-use disorder, and of course there should be. But for some of you probably looking at this video, you're like, "Well, this guy is depressed. Why is he on this high dose of dilaudid, potentially?"

Again, when we think about risk, we're thinking about the entire continuum of what's going on in these patients. This gentleman was previously on buprenorphine, on a relatively low dose before he had this compression fracture, being weaned off opioids entirely. And part of the reason he was on buprenorphine was because of his respiratory status. So again, this is a dilemma because your hand is forced with someone who has a new problem.

(Video played and transcribed.)

"I've taken Exalgo, extended release, 32 milligrams, as well as up to 3 2-milligram dilaudids per day.

"And does it help?

"It helps immensely."

DR. MARKMAN: So he's on this high-dose unit formulation that we're talking about today. He's also on some lower dose unit formulations for this problem of axial predominant low back pain in the setting of compression fracture, with osteoporosis as a consequence of steroid exposure to treat graft-versus-host disease, which was a consequence of his treatment for leukemia, which was superimposed on a chronic low back pain syndrome for which he had lumbar fusion surgery a decade earlier. So that's the layering of comorbid conditions you heard about earlier today.

(Video played and transcribed.)

"So if only a small dose of dilaudid were available, like a 2-milligram dose or a 4-milligram dose, how would that effect you?

"That would substantially change my life and put me in serious pain. It would reduce my ability to enjoy life.

"But you could still take the medication.

You just couldn't take the 32 milligrams at once.

"Right.

"So would that be a problem for you, if you had to take 16 of those 2-milligram pills at once?

"Yes, it would because the stable of getting a 32-milligram extended release, the stability of that, I'm not getting highs and lows of taking the meds, and it's a steady coverage of the pain.

"Why is that important?

"It's very important because when the pain comes back, one pill doesn't take care of it. It's 2 or 3 down the line, and you finally catch up to it. So the 32-milligram is extremely important. It maintains a nice even flow."

DR. MARKMAN: Again, I want to say one thing about that comment. Obviously, there's a lot of uncertainty about the relative benefit of short-acting versus long-acting opioid formulations in terms of efficacy in this balance, and I think that's an important research gap, that we still don't know relative advantage. But this is obviously anecdotal support for having a

long-acting formulation.

But the deeper question that's relevant to us today here is the comments I think on the diagram you saw on decision analysis on slides 21 through 23, slides 8 and 9 of Dr. Eggers' presentation, is that if he were on 2-milligram pills, he'd have almost 600 pills probably that he would need to be prescribed on a monthly basis, and what would be the unintended consequences of prescribing some fraction of that versus putting 600 pills out there.

As a clinician, that would be something that was deeply concerning to me. Obviously, with buprenorphine and many other meds, we try and reduce the amount of dose units in circulation because our concern is that's a risk factor for unintended consequences in non-patients as well as patients. So that's one of the things, obviously this committee has to balance today.

This is a patient, obviously, who's on a high-dose unit formulation. He needs more frequent and more rigorous monitoring. He needs closer

attention to his mental health status. There are a lot of comments, I think, we're going to hear about benzodiazepines, but also these folks are on muscle relaxants: tizanidine, baclofen, Flexeril, cyclobenzaprine, if you will.

I think, obviously, it's the totality of these drugs which obviously increase the risk. There's going to be a question, obviously, about how specific the pathology has to be as an indication for opioid therapy. Obviously here, I've given you a case with a very discrete focus of nociceptive pain and a little bit of neuropathic pain as the rationale for therapy. But I gave you this case for that reason, in part, because I wanted to make it clear. I'll show you others where it's far less clear.

Function and quality of life. Well, these are, again, points of controversy. Analgesics are, first and foremost, pain relievers. And if he told me that this allowed him to function better in so far as he wanted to sit comfortably and do something on his couch, to me that would be an

adequate level of function. But there's obviously diverse point of views on what a functional improvement is and how important that is; what's the primacy of that.

Then again, there's the consideration of tapering this gentleman back on to buprenorphine or using buprenorphine to taper him off entirely once he's through this acute compression fracture. He was actually incredibly annoyed with me at this visit in the early part, right up on my face saying, "I wanted you to give me an epidural steroid injection for my back pain, and you wouldn't do it, and I'm still upset about it."

The reality is that giving a patient like this, on high-dose steroids, a steroid injection, who is having compression fractures, the long-term risk of that are, in my opinion, untenable. So having to explain that to him as well kind of underscores the complexity of all the trade-offs; not just of opioids, but of all the treatments.

Let me segue to a second patient, and this is a different world of risk and complexity. This

is an 88-year-old woman with chronic neck pain and left-sided hip pain.

(Video played and transcribed.)

"Where is your pain? What part of your body?

"Part of my body is in two parts, especially between my shoulders and on my back, and then on my left hip.

"And what does it feel like in your neck?

"It is just pain there right now. It just hurts.

"And how would you describe the hurt? Does it tingle, or burn, or is it throbbing?

"What was the first one?

"Tingling, burning, throbbing. You tell me. What does it feel like in your neck?"

DR. MARKMAN: So that's the painstaking work that goes on in pain clinics right now all over the country, that people are trying to get a sense of what someone's going through. And she's looking at me like, "What? Why are you taking my time with these questions?" Right?

So what I want out of that and what I'm trying to understand is obviously different than what she wants out of this visit. She's got -- you can't see in her hand, but you'll see in a moment -- this long list of questions, this wrinkled piece of paper, which she's been developing over the last 8 weeks or 6 weeks since I last saw her, with all of her questions that she wants to get through. Why am I asking her about tingling?

So again, this is part of the complexity of teasing this apart. So let's just look at her situation. We heard about multiple comorbid conditions in a couple of the presentations today, but let me just bring this to life in this woman.

For those of you who don't look at these images all day long, your view here on your left is obviously a sagittal section or a sideways cut, a T2-weighted image of the brain and the cervical spine, and she's facing this way outdoors. What you see here in her cervical spinal cord is this big white area, which spans several segments.

She has a very large syrinx in her cervical spinal cord. That's a collection of spinal fluid, which is really just like a little water balloon, which is pushing on all of the fibers. Remember, your cervical spine is about the width of your pinkie in its diameter, and she's got this water balloon which is expanding there, stretching all those fibers in the central part of the core, which are what really mediate a lot of the nociceptive experiences we have in our lives, below our waist and above.

She is really having this constant sort of expansile mass, which is liquid expanding. Here is the axial cut in that middle view. You can see that there's a big white thing. Basically, you can see the syrinx is pushing all the fibers of the spinal cord to the side, to the rim, so the big white part in the middle is that fluid collection.

Then of course, in her hip, this hip has been now on its third revision for her hip pain, which is obviously more of a nociceptive syndrome compared to her neck pain, which is probably more

neuropathic depending on how you think about mechanisms, to the extent that that's even relevant here.

She's got multiple complex problems. But the biggest risk in her case, what terrifies me -- she's not actually on particularly high-dose opioids. She's on 60 milligrams of oxycodone a day, which is high for her. That's a very high dose. It doesn't meet some threshold. It's 90 milligrams of morphine equivalents, but it doesn't make a lot of the cutoffs in discussions we've heard today.

I won't show you the most terrifying movie of this woman. It's watching her walk because she's going to fall eventually, and you know that. She's got a loss proprioception in her feet. She's deafferent because of syrinx. She's got 4 other replaced joints below her waist in addition to this hip that I've shown you, and she's on high-dose opioids, and she's going to fall.

She's not going to develop an opioid-use disorder, I don't think. I think she's at

extremely low risk for that. She's got no personal risk factor. She's got no familial risk factors, but she is going to fall eventually and that's going to be my responsibility.

(Video played and transcribed.)

"Do the medications help?

"Yes, it helps, as long as I can get it quick enough. I try to get it, but it takes about an hour after I take it.

"What's your total dose and how much do you take a day? How many pills do you take?

"I take 6 pills.

"Of oxycodone.

"Of oxycodone.

"What dose?"

DR. MARKMAN: What?

(Video played and transcribed.)

"I take 1 every 3 hours.

"How big is the pill?

"It's very small. I don't know how to describe it, but it's very small.

"Do you know how many milligrams are in the

pill?

"I have not looked at that. I haven't studied it.

"Do you know how many there are?

"Ten.

"Ten. So you take 60 milligrams pills per day?

"Yes.

"And you take them every 3 hours?

"Yes.

"Does it help?

"Yes, definitely."

DR. MARKMAN: So she's on this very short interval of dosing, which we have tried mightily to get her off. We wanted to try her on fentanyl, and she's been on buprenorphine. She's failed them all. They've all been disastrous. She couldn't tolerate them. She was too confused. She was too dizzy. She was too unsteady. So we've had to live with the fact that this is the right regimen for her.

I don't feel great about writing this big

prescription every month. In fact, I feel really ambivalent about doing it because I know that ultimately it's not going to probably end well, because her biggest risk is a fall. But I don't really have much choice, and here's why.

(Video played and transcribed.)

"Is this a stable dose or the dose has been changing?

"No, it's been a stable dose for quite -- oh, I don't know how long.

"How many years would you say?

"(Laughing) Oh, it's been 2 or 3, or more, at this dose; about 2 or 3 I think that I've been on oxycodone.

"What would your life be like without it?

"It would be horrid. It would be in a lot of pain, because I can tell when my -- begin the need. When my timing is getting ready for another pill, I can tell because I'm hurtin' so bad. I don't know any other way to do it, but maybe you do.

"I don't.

"So I just will have to get along the best way I know how.

"Well, you've been doing that a long time, and you've been doing a beautiful job.

"Well, thank you.

"Is this a stabled --"

DR. MARKMAN: Obviously, this is about the cumulative burden that we see and I think which really presents these dosing challenges for many of us who take care of patients every day and are in the room with them with their family members, and trying to deal with the fact that you often don't just have low back pain, as you saw there. They've got at 66 percent, but they've also got 66 percent arthritis, and they have all those other conditions at the same time layered on one another.

So let me just talk a little about variability. Obviously, these first two cases are sort of a plea for latitude, for the complexities of decision-making, all those different ideas which are going through your head. The one most replicated finding of the 20th century, and of the

most recent century in pain, the only thing we really know for sure with any degree of certainty is about variability, variability of the pain experience. That's really been the great lesson of all of our scientific studies.

So I think when you hear resistance to a cutoff or a threshold, it's an appreciation for that fact; that's our most replicated finding. So a threshold which says it's going to be cut here seems to, in some ways, be a critical tension with that idea.

Let me just unpack this idea just a bit more. This is a slide that's a cliche at this point. It's almost three decades old. It's a study, one of the original studies, looking at patients with MRIs with their spines who had all sorts of pathological findings, but it turns out they had no symptoms. They didn't have any pain intensity.

Obviously, I've showed you two images of patients previously, one with a compression fracture, one with a cervical syrinx, where I made

the claim to you because of the correlation of their symptoms, or at least I endeavor to do this. Like I convince you, I try to convince myself that those images correlated with the pain experience the patient was having. But the reverse is also true. There are many patients who've got findings who've got no pain at all, and that's the complexity of the rule.

This is a wonderful registry study out of New York City. We know that opioid dosing is highly variable. This is a registry through the New York hospital system recently published in the Journal of Pain, looking at patients who seek outpatient care for complex chronic pain problems who do not have cancer.

This is just a glimpse of what the spread of opioid prescribing is for these patients. Just look at the standard deviation there. That just gives you an appreciation for the diversity of range of drug that people are on.

We also know that analgesic benefit in low back pain syndromes, about which there was a

question earlier, varies with baseline affect. This is an important study by Ajay Wasan of Pitt showing the reduction in pain intensity, from being on a medication, an opioid medication, is changed by your baseline level of affect, if you have high negative affect versus low negative affect. The take-home from the abstract of that paper is the benefit-risk considerations in chronic low back pain patients with high negative affect versus low negative affect effects are distinctly different. It has nothing to do with the drug.

So differential treatment response to analgesic medication is not all attributable to the drug itself. Everyone here knows that.

Here is a recent analysis we did, a post hoc analysis, of the end of the open-label phase -- excuse me. This image is a figure from the end of the open-label phase of the development or the pivotal study for an abuse-deterrent opioid, oxycodone. To me, this is one of the ways, as a clinical researcher, I think about how variable opioid dosing because you have this world of

patients in the community with fair levels of high pain intensity.

They decide to enter a clinical trial for a novel abuse deterrent opioid to be therapeutically optimized during the open-label phase. And even in that optimization process, they all come out with look at these range of different doses.

Why don't these patients all self-titrate in this free open-label titration period with the same dose? They're all over the map, and these were patients who were not opioid naive. These are patients who were previously exposed to short-acting oxycodone, who are going to be put on a long-acting, abuse-deterrent opioid formulation of oxycodone, and they just self-titrate all over the map.

This is the best study of this question, the most rigorous one. This is a slightly analogous population. This is a recent work by Jen Gewandter, Mike McDermott, and other folks at Rochester, looking at 4 clinical trials in cancer breakthrough pain of rapid-acting fentanyl, and

looking at the 6 active treatment episodes with fentanyl and the 3 placebo episodes.

These bubbles, these blue bubbles, are each an individual patient. What you see here when you're looking at the treatment effect on the Y-axis is that there is a range of these patients. There is a treatment by patient interaction here when you compare it to placebo. This is another way of thinking about this issue about variability of drug response, so it makes it hard to establish a cutoff when we have here placebo-controlled experimental evidence, again, answering this question about variable drug response.

Again, it is hard to show a dose-response curve with opioids, and the reason is the following. Obviously, patients who are on too much dose get too many side effects, and they drop out of studies. Patients who are on too little dose have inadequate pain relief, and they drop out of the studies.

The way I think about this as a clinical researcher is in the ideal world, that trade-off,

that Y-axis of goodness where you have high efficacy and high tolerability of an opioid, would be a really long, flat amount. And there would be a big range of doses that got that optimal balance at the top, and everyone would kind of end up on that dose; that kind of fits the one-size-fits-all dream of opioid treatment.

But this is what it looks like when you look at these trials. You've got patients who are each on their little cliffhanger of tolerability because of constipation, sedation, itching, nausea, don't like the way it makes me feel in some generalized way, and relief. And you're sort of this hairpin; you're not on this amount. These patients are all over the map, and this adds to the complexity.

I just want to say something about titration. Obviously, to the anesthesiologists in the room for whom this is the central methodological axiom of their entire practice, this is obvious. But it's important to realize that titration is the centerpiece of pain management, especially when it comes to medication.

Let's listen to this gentleman, a 58-year-old gentleman with horrific left-sided throat pain.

(Video played and transcribed.)

"I had a flare up when I tried to go off the medication.

"That was around your daughter's wedding?

"That was for my daughter's wedding. I just wanted a day to where I felt straight because I had to give her away, and I had a flare up the next day."

DR. MARKMAN: So he wanted to feel straight. This gentleman is not on an opioid. He's on oxcarbazepine. He's on Trileptal. The trade-off of tolerability for pain relief is not unique to opioids. We're going from room to room, patient to patient, and in some rooms, it's about opioids, but a lot of other rooms, it's not.

(Video played and transcribed.)

"I had had a flare up. I wanted to go back a little bit. I've never been happy with the side effects of it. As I went back to about 400, I had

a flare up of the symptom.

"What happens when you have a flare up? What's it like?

"I start to get the severe jabbing pains in my throat.

"Where? Point to where you get it.

"It's basically under my jaw on my left side. It feels like it's in the back of my throat. It's a very sharp pain. Happy to be on the medicine to take care of it, but I prefer to be off of them if I could."

DR. MARKMAN: That's true of all the patients we see. I mean, virtually all of them don't want to be on this medication. They're very clear. They're very reluctant, whether it's opioids, or in this case, whether it's oxcarbazepine.

(Video played and transcribed.)

"You had to increase the dose recently to get it under control?

"I increased it by increments of 100. I went back up actually, and I am now at 800

milligrams.

"Do you like being at a higher dose?

"I don't. I don't like to the symptoms.

"Why not?

"I like feeling normal, and I'm not normal when I'm on the dosage. It's hard to focus. I have some motion sensitivity. I'm not necessarily stumbly and fumbly, but it feels like that might be -- on higher doses, that might be part of it.

"Have you had any falls?

"Just one mishap where I was -- when I was working, I was sitting on a toolbox working on some electrical outlets --"

DR. MARKMAN: Terrified, right?

(Video played and transcribed.)

"-- and I slid backwards off of it. But nothing like falling and get hurt or anything."

DR. MARKMAN: No, you couldn't get hurt that way. Fall off an electrical box at a construction site, no, nobody gets hurt that way; of course. So this same issue -- this is not an opioid -- tolerance; withdrawal; dose escalation;

side effects; doesn't like the way he feels; dizziness; the risk of a fall in the workplace, all the same issues.

So these are not necessarily opioid specific trade-offs; these are trade-offs -- now again, this is incredibly an important, serious point. We are acutely aware of the lethality of opioids, and that is not to liken them to oxcarbazepine because the epidemiologic signals have nothing to do with one another with regard to community risk.

So again, I make the parallel not to suggest to you that these are equivalent risks, but only to say that these are the same issues, which we're balancing across many medication classes which act centrally. Now, obviously opioids have very specific risks. I think there's more work to be done, and we heard about this, and more work that will be done with new authority by the FDA, to think about how we can think more deeply about, again, who do you preserve access for and who is at greater risk for self-harm or community harm.

I think we need methodologies to reduce

channeling bias in these observational studies, which are incredibly important and have changed the way we've all practiced. Again, we need to think about how to design a prospective low dose versus high dose, free titration study, where we have an optimal design to detect the adverse events we care about. I think that's where we have to go.

One more slide -- or two more sides, excuse me, and I'll be all set. I just want to leave you with two patients with low back pain. I'm not going to share with you any image of these patients. This is patients who've had prior lumbar surgery. This is the most common reason among the low back pain world to be seen in the subspecialty pain management clinic in the United States. We have an extraordinary high rate of lumbar surgery in the United States.

I'm just going to finish with these two patients who have no acute pathology to show you but are living with this incredibly heavy burden.

(Video played and transcribed.)

"The side effect you have is constipation.

"Yeah, and a little bit of tiredness, but it could be age, too (laughs).

"What kind of cancer do you have?

"Myeloma, multiple myeloma.

"Do you have any pain with the myeloma?

"Yeah, but that's scared [indiscernible]. That's all over. That's nothing to worry about until it hits. That's all."

DR. MARKMAN: She lives in Le Roy, New York, the birthplace of Jell-O. She has an aviary with 300 birds in it, which she manages. She needs to get on with her life. She has no time to waste with me every other month to see me for a refill, and here's her frustration.

(Video played and transcribed.)

"The pills do not cover the pain a hundred percent, but it makes it livable. And then I get off my feet and lay down, and put a heating pad on, and that's how I survive. But as far as people cutting out your opioids, they're just going to drive more people to the street. And they will go on the black market for their pain medicine.

"Why?

"Because they're in pain. If you take it away, I'll tell you right now, if someone were to take mine, I'd be on the market, because it isn't fair. Your politicians and all of these big whigs, they're in their own little world because they don't have the pain.

"If they had the pain, they would know what we are talking about. But because they haven't suffered the pain, the back pain, they have no idea. They're just going by statistics. And what good is it? What about talking to people that are on the drug? They've been on it. They aren't doing harm to it. They're taking it as prescribed.

"How long have you been on it?

"Oh, 10, maybe 10 years."

DR. MARKMAN: So again, I worry that in the same way with the development of abuse-deterrent opioids, we've had unintended consequences; so, too, could changing pill counts and other dose forms lead to other intended consequences.

I'm not going to talk about opioid-use

disorder, but I will say that anyone who has their dose of opioid reduced by 25 percent or 50 percent, who's been on it for 3 years, you're inducing an iatrogenic opioid-use disorder. We all know that. You are replicating all of those features.

I want to finish with one last patient. She has a very slow motion tectonic form of cauda equina syndrome. Just imagine your garden hose being slowly kinked, but it's her lower spinal cord. She's plegic in the lower extremities now. She's lost bowel and bladder function. She's on buprenorphine. She's a refugee from the northern part of New York near the Adirondacks, who couldn't move to our region until her son found a provider who was willing to prescribe buprenorphine for her, and her gabapentin, but mainly her buprenorphine. These are the decisions that families are making to seek care.

(Video played and transcribed.)

"I obviously would love to have a straight spine, and be out of a wheelchair, and go back to doing things that I did when I wasn't -- I think

I -- I have a fairly high pain threshold, I think.

"I do, too.

"When I say I need medication, I don't do that easily. I don't -- it's not a stigma, but I just don't like medication. But I recognize I need it for some things, and I'd be stupid not to take it. So I don't think anybody arbitrarily is saying to me, your dose is too high, reduce it, without being aware of my situation, as Steve said. It's the wrong question, and it's the wrong action."

DR. MARKMAN: She's obviously in a very precarious position. Obviously, she has marked scoliotic deformity. One of the reasons she's on buprenorphine obviously is for the respiratory issues, but also for pain control.

DR. HERNANDEZ-DIAZ: Dr. Markman, last one, please.

DR. MARKMAN: I'll just finish here. We're all set. I'm just going to say some final considerations, is to think about, obviously as you will, the very building complexity of drug response; obviously, the pain conditions in

general; the need for studies, I think, of novel opioids, which are abuse deterrent but also are enriched for the populations most at risk for harm, patients with substance-use disorders and risk for that.

Again, there's a major evidence gap with regard to the relative benefit of long versus short-acting opioids, even though they've been around, as we've heard, since the late '80s. And I really think that one of the ways to get clarity around the trade-offs here is to understand better the potential benefits, if there are any, of long versus short-acting formulations. Thank you very much.

DR. HERNANDEZ-DIAZ: Thank you, Dr. Markman.

We'll now continue with an invited guest speaker presentation with Dr. Michael Rowbotham.

Guest Speaker Presentation - Michael Rowbotham

DR. ROWBOTHAM: Thank you very much for inviting me. I'm going to cover two things, some aspects of clinician care of patients with chronic pain, and then I want to review some of the

literature, published and unpublished, that gets to the issues of number of pills one might take a day and higher strength opioids.

I'm going to use a pointer for some of these. I'll use it on this one, and hopefully people in the back can see that.

I have something of an unusual background. When I was a medical student at UCSF, I got interested in psychopharmacology in my last year, and then I went on to do a fellowship in the drug dependence research lab, where we studied things like high-dose naloxone, intravenous cocaine, and just about all manners of illegal substances.

I went on to do my internship at SF General. That was the first year of the emergence of the AIDS epidemic, and then from 1982 to 1984, as I was deciding whether or not to do psychiatry and neurology, I was the medical director for substance abuse services at SF General Hospital. I had an average of about 120 patients in long-term methadone maintenance and anywhere from 80 to 100 in a 21-day methadone detox program, while

continuing my research studies.

I went on to do my neurology training and then a research fellowship with Howard Fields at UCSF as the UCSF Pain Management Center was forming, and went on to be the associate director there for several decades and started a large pain clinical research center.

Some of those studies that we did there were on opioids, including the first placebo-controlled trial of intravenous opioids with lidocaine and placebo comparators for neuropathic pain, postherpetic neuralgia, and then a longer term trial for levorphanol for different kinds of neuropathic pain, both central and peripheral neuropathic pain.

Then I'll show you some data that's still unpublished about what happens if you start incorporating experimental pain models to look for opioid-induced hyperalgesia. I've transitioned. I'm now the chief research officer for one of the 10 largest healthcare systems in the country, Sutter Health, where we have 3 million patients in

care, and of course many of them on long-term opioids.

This is not a new problem. This is from 1870 as injectable morphine was becoming available. The question was raised about does morphine encourage the very pain it pretends to relieve? So not a new topic. Of course, the current opioid epidemic is at least 18 years old, the 2001, the cover of Newsweek, and then in 2003, the cover of Newsweek, both about the problems with OxyContin, Vicodin, and other prescription opioids.

As I observed, even back to the days of running the substance abuse services at SF General, there was a pendulum swinging even then, where there would be a period of time of relative permissiveness about using opioids to something much more focused on drug control, and where it had been in this latter phase where the pendulum has swung from the pain is the 5th vital sign and relatively liberal attitudes towards opioid prescribing in the early 2000s, to now much more concern about diversion of drugs and all the topics

that are being discussed at this meeting.

Just to sum it up, opioids are effective, and we saw some that data today. The article by Busse in JAMA last year is really quite useful, and it's a meta-analysis and shows that opioids are effective compared to placebo. In limited studies, which have been compared to antidepressants and convulsants, this also shows efficacy.

The efficacy is relatively small. For longer term use, it doesn't hit it out of the park, but it's certainly very useful and a type of treatment for which there's not already a non-opioid substitute. The caveats are that there's little efficacy data spanning long time periods, 6 months or more, for opioids, but also not for any other drug class. So it's not like you could look at studies of gabapentinoids or antidepressants for chronic pain and come up with higher quality data over long periods of usage.

It's a difficult class of drugs to study because the dropout rates in clinical trials of opioids I think are substantially higher than with

any other drug class. It's hard to get people to enter a trial of an opioid, and it's hard to keep them in a trial of opioids.

Many patients can't tolerate the mood or other effects, and they tend to discontinue opioids relatively quickly. But the stigma of being on opioids and often very intense family pressure leads patients to actually self-discontinue or try self-tapering, and they will often do this without telling their physician and sometimes even will taper themselves down quite significantly. Some of it is just testing the waters. They want to believe that they're not addicted, and if they can reduce their dose downward for a period of time, that convinces them that they don't have an opioid-use problem.

Then of course, as Dr. Markman pointed out, it's hard to find prescribers. They fear licensing board investigation, and they fear the reputational damage that goes along with being viewed as a physician who will prescribe opioids. I think these last two things are underemphasized, both the

patient perspective, the stigmatization, and the physician stigmatization.

But physicians are a big part of the problem. We know from the presentations today and the abundant literature on this that exposure to prescription opioids increases risk for abuse, overdose, and other adverse events in a dose- and duration-dependent manner. The prescribers are directly or indirectly the source of most misused opioids. Opioid prescribing often continues after abuse is diagnosed.

So we know that the opioid dose does predict -- perhaps not as strongly as one might expect, but it does predict overdose risk. However, decreasing the prescribed opioid doses do not, at least to me, seem to be proven to actually reduce the risk. So the number of opioids prescribed has been steadily going down the last five years, but that's not necessarily through tapering patients who were already on opioids. It's just that physicians, when they start patients on opioids, they start with lower doses, and they

don't allow patients to titrate up as high as they did before.

Something that was hinted at in some of the earlier morning presentations is that opioids plus benzodiazepines, or other sedatives and alcohol, are potentially a very toxic combination. We knew this when I was running the methadone clinic. We would get patients stabilized on opioids and then gradually lose them, sometimes fatally, to benzodiazepines and especially alcohol. So the opioid use could be controlled, but not the other drugs. There have been a number of studies of benzodiazepines, and they are not analgesic. So they increase the risks of opioids without adding to the analgesia. That's not a good combination.

The other lesson from some of the methadone clinic experiences is that urine testing can be utilized, but it's very difficult to utilize, especially in an environment that isn't so tightly regulated as a substance-abuse clinic. However, if as a clinician, you're concerned about a patient, it's both legal and ethical to ask them to come in

frequently, to give them only very short term prescriptions, because you need to see them. You need to have that face time that Dr. Markman was showing us in his video clips.

Why is it so hard to demonstrate long-term efficacy? This is a study that Steve Quessy and I did and published over a decade ago. What this shows is that the placebo response doesn't actually stabilize. So when one looks at clinical trials -- and this is of any type of compound in a placebo-controlled trial -- it tends to actually increase over the duration of this study.

On the vertical axis is the change in pain from baseline, so higher is a greater change in pain; and then on the X-axis is the number of weeks in this study. As you can see, when you get to even studies that are 18 or 19 weeks long, a placebo is doing quite well, and it's continues to do well. Of course, since you have to adjust for the active drug compared to the placebo drug, the placebo control, that just makes it harder and harder to show benefit.

So what you see in some of the trials of drugs is an early benefit of active over placebo, which is gradually lost over time, not because the active drug, the experimental drug, stops working but because placebo catches up to it, and eventually the difference between the two is no longer statistically significant; so very important.

Tolerance. Dose escalation or loss of analgesic efficacy during long-term treatment of -- and what I'm going to talk about is chronic non-malignant pain. How quickly does that develop? This is another study that was done. This is in healthy volunteers. It probably would be a little hard to do this study now, but at the time it wasn't.

We gave them two injections of subcutaneous morphine, 6 milligrams, so they got a substantial dose over the course of each session. One group got placebo for 4 days, and then on the 5th day, they got morphine. The other group got morphine for 4 days, and then placebo on the 5th day. We

incorporated BTS, which is a brief thermal sensitization model. It's a cutaneous hyperalgesia model that's induced by heating, because these are healthy volunteers. They don't have pain, and they've never been exposed to opioids.

This is what the data shows. What you can see here is this is the reduction in the hyperalgesia, stable the first 2 sessions, starts to decline, and declines more. We would have liked to have done this study over 7 or longer days, but that would have involved keeping the study site open over the weekend, which was not going to be allowed by the university.

We saw evidence of tolerance over 4 days that approached but didn't quite reach statistical significance. It starts to occur by day 4, and it seems like it's more complete once one gets out to a few weeks to a month.

What about dose escalation and analgesic efficacy during longer term therapy of chronic non-malignant pain? This is a classic study, 1996, [indiscernible] working in Canada. This one I

think is very important to take a good look at. With this one, it's a crossover trial. It wasn't part of a registration program. These were patients with chronic pain, most of whom were taking low-dose codeine when they entered the study.

Here, the top is the placebo. Not much happens during the titration period. Not a whole lot happens during the 6 weeks of stable dosing. The morphine group goes down, and then over the next 6 weeks, the pain scores start going up. Then the patients wash out, and then they cross over.

What you see in both periods of this study is that morphine reduces pain, and then that pain reduction is lost during stable dosing. So it's the opposite of placebo. It's not getting better, it's actually getting worse over time. So that's suggestion of tolerance, analgesic tolerance, in this study.

This another study that I did, and although it got a lot of attention at the time, it's not a placebo-controlled study. It's a dose-response

study. Therefore, it doesn't usually end up in any of the meta-analyses because there is no placebo control.

Here patients were given 4 weeks to titrate to what they felt was the right combination of pain relief and tolerable side effects. We put some guard rails on there so that people couldn't get up to the maximum number of capsules of 21 capsules a day. This is with levorphanol, and at the time we used levorphanol -- because it's a very potent opioid that can be dosed 3 times a day, and no one had ever heard of it, even though it had been around for decades already, so it didn't have any stigma. Both the patients and their regular physicians didn't have any particular attitude about levorphanol.

Patients were treated for a number of weeks and then went into a taper. The capsules were very tiny. They either contained 0.15 or 0.75 milligrams of levorphanol. Now, if you just get a levorphanol pill, it's actually 2 milligrams. So even the high strength group are being given a

fairly small number with each dose.

One looks at the data. This shows all the classic problems with opioid trials. First of all, when you look here, the number of patients steadily declined. We started with 81; we ended with 59. That's actually pretty good because some opioid trials have lost almost half of their patients by the end of the trial.

The second thing is that there is a difference between the group given the low strength pills and the group given the high strength pills, but the high strength group tended to have some problems with agitation. They had a lot of side effects. The key thing is -- the big difference is the low strength group took a lot of capsules. So what they did is they made up for the lower number of milligrams of levorphanol in each capsule by just taking a whole lot more of them.

The dosage limit was 21, and they got up to more than 15 capsules per day on average. That just shows that if you reduce or if you eliminated the really high strength ones, patients, if given

access, will just take more of the low strength ones to get the same amount of pain control. Then of course, the actual number of milligrams was really quite variable, especially in the high strength group.

Let's turn to what is a topic that is frequently cited in the lay press and also in opinion pieces in the scientific literature but has actually received very little formal study. That's the question of opioid-induced hyperalgesia. It's thought to be a state of nociceptive sensitization caused by exposure to opioids.

It may actually be through a non-opioid mechanism. The exact mechanism of opioid-induced hyperalgesia is still uncertain. It's fairly easy to demonstrate in animals through fairly complicated regimens that often include precipitating withdrawal with naloxone. But it is frequently invoked as a contributor to addiction, dose escalation, and overdose.

There is some historical data going back many decades. The problem with those studies is

that some of the patients were on phenothiazines or other confounding drugs, or they were given extremely high-dose opioids, so it's hard to interpret these anecdotal case reports.

There's also some suggestion in the literature that patients who have been on long-term methadone maintenance or long-term opioids do have lower thresholds for experiencing pain due to cold and other stimuli. In other words, something called the cold pressor test, which is basically just sticking your arm in an ice bucket filled with water until you can't tolerate it anymore, that they're a little more sensitive to that, but in humans there's really little or no perspective data.

I won't go over the Chu study, which was published in 2012, where they found tolerance to morphine at an average dose of about 80 milligrams of morphine a day but no hyperalgesia, so tolerance without hyperalgesia. Then I'm going to show in the last couple of minutes some data from a study that we did again with levorphanol.

This was a study that was intended to be a pilot study for a much larger trial. It proved to be extraordinarily difficult. It took years off my life, I'm sure, to try and do it; hard to recruit patients; hard to get them in; and hard to keep them in for 6 months.

What we did is if they were already on opioids, we did not mess with that. All they had to do was to stay on the exact same dose with the permission of their prescribing physician who we were in regular contact with. Then we added levorphanol to that, again, with a titration period and then 20 weeks with a fixed dose. The red arrows show 5 observed dosing sessions that incorporated this same brief thermal sensitization model to heat.

I won't spend any time, really, on these groups statistics, but suffice it to say that we had the usual high dropout rate. We were able to recruit between UCSF and UC San Diego, 30 patients, and only 17 of them completed through visit 9. The rest dropped out.

There was a modest reduction in pain. They didn't become hypersensitive to the heat stimuli over that period of time, and every time they came in for an observed dosing visit, they typically felt better. Their pain was better during that observation period.

Here's what we were looking for. Really, the individual cases, were there any patients who developed both tolerance and hyperalgesia? We called it deterioration. If their pain scores actually went up instead of down compared to baseline, that would be clinical deterioration. And if there area of hyperalgesia to the thermal stimulus actually went up instead of down, then we called that hyperalgesia.

Also, the perceived reduction in pain during the observed dosing session also decreased, and we would consider this patient to have both tolerance and opioid-induced hyperalgesia.

We found three examples that one could maybe classify as this out of 17 and during a very long and arduous protocol. We tried to get this study

funded to do a longer term study, failed a few times, and I was happy to not continue to try because that would take even more years off my life trying to do a much larger study like this. Now I think it would be impossible to do such a study because patients were able to titrate up to well over 300 morphine equivalents per day if they were in the higher strength levorphanol group.

Here's are some take-away messages. Who should receive opioids? I think as we saw these, the patients who are on higher dose long-term opioids are really complicated patients. It's rarely a simple, single, straightforward diagnosis, but usually a complex constellation of problems that are just difficult to manage or impossible to manage through non-opioid means.

The second part of this first sentence is perhaps a little more inflammatory by saying they're not that different from methadone maintenance patients. I'm not saying personality wise, they're the same or anything else, and I certainly am not advocating that chronic pain

patients be put in a methadone clinic type of environment because that's pretty unpleasant.

Some of the guard rails that need to be put in place to both protect the patient and, in a sense, to protect the prescriber does require very close management of these patients, and they need to be seen frequently and really listened to in order to make sure that things are going well.

The hardest part of getting a patient to taper off opioids is to start, and it takes a very motivated patient to even be willing to entertain that idea. There has to be a reason for them to want to taper and to stick with it because it's unpleasant.

Clinicians struggle to set limits and to monitor their patients closely. It's not easy to find the time to spend 30 to 45 minutes at every clinic visit to do all the talking and monitoring necessary. Physicians are often slow to recognize dependence and abuse and may not fully recognize the risks associated with combinations of opioids and drugs like benzodiazepines.

I covered a little bit about opioid analgesic tolerance. It probably takes a week or more to really develop, and it's probably pretty well developed by a month. The concept of opioid-induced hyperalgesia, every time you read it in the press, I want you to just think about how little data there is to back this up in humans; easy to describe, easy to invoke, but really not well supported by prospectively gathered objective data. Thank you very much.

DR. HERNANDEZ-DIAZ: Thank you very much.

We will now continue with the an invited guest presentation by Dr. Mary Lynn McPherson.

Guest Speaker Presentation - Mary Lynn McPherson

DR. McPHERSON: Good morning. Thank you for inviting me. I'm very appreciative of this opportunity, and I'm especially appreciative of your including the perspective of how any potential action you may take would affect people with a serious illness or a life limiting illness.

My name is Lynn McPherson. I'm a professor at the University of Maryland School of Pharmacy,

and I've been practicing in hospice and palliative care my entire career, as well as ambulatory care. When I was first asked to do this, I thought, well I could kind of noodle on my perspectives about this, and then it occurred to me that I actually have access to a fairly enormous drug utilization database from the fourth or fifth largest hospice in the United States.

This is Seasons Hospice and Palliative Care. This is their catchment. They're in 19 states. They're a pretty large database. We've done quite a bit of research looking at other medication utilization patterns, aside from opioids.

But nonetheless, this database looks at patients who were admitted to this hospice after January 1st of 2012 and discharged by death by December 31, 2016. A very small number of patients do graduate from hospice, at least temporarily, and eventually do find their way back; 78,000 patients met this criteria, so this is a big old database here.

I did exclude people who are getting

parenteral opioids. I didn't think that was really relevant to this conversation today, and I did exclude the PRN opioids because it's kind of all over the place. So basically we're looking at scheduled, non-parenteral opioids with this data. If it was a combination like Percocet, for example, I just included the opioid component.

The average age of the patient population, 77 years old. A little more than half were women. This is the basic demographic slide. As you can see here, we still struggle with getting non-white patients into hospice. It's a continuing struggle for all hospice programs. You can see our payers are pretty heavy on Medicare and Medicaid.

On the right, you'll see it's interesting, looking at 5-year period. Cancer was represented by 45 percent of the patients, and that's going down dramatically, which I'm actually happy to see because cardiology diagnoses are increasing, particularly over the last couple of years. Cancer is less than 30 percent now on hospice.

The bottom table, the little chart there, is

important. Our mean length of stay in hospice is 18 days, so clearly, it would be lovely if we could get people into hospice quicker. Median length of stay ranges from 6 to 60, looking at the interquartile range.

In looking at this, I did pull an article from 2004 where they categorized looking at opioid use in home-based hospice patients published in 2004. They had categorized it as shown here, oral morphine equivalents, as low, being less than 59 milligrams a day, 59 or less; moderate being 60 to 299; and elevated doses were high and very high at 300 to 599, 600 or higher. I guess in the current climate, perhaps next time I run this data, I will do a shift to the left, and I will have low, high, super high, and crazy pants high.

(Laughter.)

But using this model -- just stick with me here -- I did write the only book in the world on opioid conversion calculations. What can I say? I love drug math. If you look at the diagram to the right here, this is the opioid conversion table

that is probably a little bit different than what you've seen in recent years because, thankfully, we are getting better data to support doing these calculations, so that's very helpful.

Using this, I extrapolated all these different categories to the other opioids that we use so that I can share with you how this data falls out. This is a very busy slide, but this is just the obligatory slide where you throw everything up here together.

Of the 78,000 patients, 25,000 received opioid therapy; 23,000 or so were calculable; and then it really culminated in about 46[000, 47,000 opioid prescriptions during this 5-year period, meeting those criteria I shared with you.

I do have the red box showing you that, overall, regardless, we do see that 52 percent of patients, regardless of the opioid, were in the low-dose category, and 44 percent were in the moderate with 2 and 1 percent, respectively, in the high and the very high.

I thought this was interesting, to look at

which dose formulations we were using in these patients. Morphine -- of course morphine is mother's milk in end-of-life care -- 21,000 prescriptions for morphine of which 37 percent were a tablet or a capsule. But as you can see, two-thirds of them were an oral solution.

We use a lot of oral solutions. You had a question earlier about the high concentrates. Even without having to go to a compounding pharmacist, morphine comes as a 20-milligram per mL, as does as oxycodone. Methadone comes as a 10 per 1, and probably the other largest medications that we use also comes in 10 [indiscernible], which even if someone's unconscious, you can put it in the buccal cavity, and they won't ask for it as you prop their upper body up.

So as you can see for morphine, and for hydromorphone, and for methadone, the oral solution actually was the preferred formulation, and the remaining 10,000 prescriptions were transdermal fentanyl.

I thought it was also interesting to look at

how much of short-acting versus long-acting tablets and capsules we use. Looking at morphine, 21,000 prescriptions, you can see, again, about two-thirds are the short acting, which makes sense because I just shared with you two-thirds of the prescription is oral solution.

Oxycodone is a little closer to 50/50. You can see the absolute number of prescriptions for oxycodone are less because the branded product is OxyContin, and we don't tend to use many branded products. The abuse-deterrent formulations we really don't use because it's an economic issue. It's far more expensive. So our workhorse drugs are long-acting generic MS Contin, for lack of a better word.

The morphine solution, the Roxanol in particular, we use a good amount of methadone. Many patients come to us on transdermal fentanyl. It's actually not a preferred delivery system because people who are very close to the end of the road tend to have pain. They could become unstable, and trying to titrate with transdermal

fentanyl is like trying to steer the Titanic. So often they'll come to us on transdermal fentanyl, and we will switch them off.

We don't really use the long-acting abuse-deterrent hydrocodones and hydromorphones for economic reasons. And even though I've listed the methadone as short acting, we know that methadone is a long-acting opioids, but what I mean by this is there is not a modified formulation that's been pharmaceutically manipulated. Tramadol, we do unfortunately see a fair amount of this being used, mostly the short acting overwhelmingly, and a little bit, the long acting.

I wanted to focus on morphine and oxycodone use. Looking at the 21,000 prescriptions for morphine, as you can see, again, 66 percent were the short acting; 33 percent were the long acting. When you look at the dose ranges, looking at the low dose, the 8,000 prescriptions is 56 percent of the morphine population with the long acting being 47 percent. Then when you look at the moderate, it ranges between 42 and 50 percent, with the high and

the very high coming in at 2 to 3 percent, and then 1 percent for the very high.

I think the bottom chart is very instructive. If you look at the dose ranges in the far-left column and look at the median on the far right, in the low-dose range, which again is 56 percent of our prescriptions, the median dose is 30 milligrams. If you look at the moderate, which is 47 percent of our prescriptions, 80 milligrams is the median dose with very little use of the high and the very high.

I think this is a very instructive slide for your conversation. I wanted to look at what are the actual tablets strengths that we are using and how prevalent is their use. If you look at the tablet strength, of course, and then looking at the short acting, 513 prescriptions for the 15-milligram morphine, which is 6 and a half percent of the morphine prescriptions, with 174 of the 30 milligrams. So this is going to be like your MSIR 15 or 30. Again, remember we use an awful lot of morphine oral solution.

If you look at the long-acting morphine on the right, you see that the majority, 42 percent, are going to be the 15 milligram, the 30 milligram, and so forth. But if you go down to where you see the 100-milligram tablet, a 100 milligrams and higher, this represents about 4 percent of all morphine tablet and capsule prescription; so admittedly, not a lot of use of the high-dose oral morphine formulations.

Looking at oxycodone, the short acting represents about 53 percent of the scripts, of the 3188 we had; the long acting, about 47 percent. Again, looking at the low dose, this is the majority of our business between 65 and 70 percent between the short and the long acting. The moderate doses are between 25 to 30 percent. With the very high, we did see about 16 percent with the short acting, 2 percent with the long acting, and with the very high, 7 percent and 0.3 percent.

So looking at the bottom table, again, looking at the far-left column and then looking at the far right, again, if you look at 66 percent of

the patients who got low dose, the median dose was 20 milligrams; 27 percent of our patients got moderate with the median dose being 60. So 93 percent of all oxycodone prescriptions were represented by the median doses of 20 and 60 milligrams.

Similar to the morphine slide -- and I think some of this data needs to be cleaned up a little bit. But just focusing, you can see we have quite a bit of greater diversity in the short-acting tablet strengths and capsule strengths on the left, but still the big winners unsurprisingly are the 5 milligram and the 10 milligram.

If you look at the right, the most common are going to be the 10 milligram and higher. So the 10 milligram long-acting oxycodone, 15 percent of the prescriptions, and so forth. If you look at the 60- and the 80-milligram long-acting oxycodone, this is 5 percent of the oxycodone prescription. We've seen this both with morphine and with oxycodone. Looking at the highest doses of the formulations that are available, it's about 4 to

5 percent of what we see being used.

Well, how about our friend transdermal fentanyl? Actually, again, this is really not one of my favorite delivery systems for a variety of reasons. There are so many patient variables that can affect patient response. We routinely get little old ladies who weigh like 80 pounds coming in on transdermal fentanyl, and it's very difficult to know quite what you're doing there.

Even though they're used quite a bit, you can see they're fairly low in strength. This is the similar slide to what I showed you for the morphine and the oxycodone. Even though 25 percent of all the transdermal fentanyl prescriptions are the higher strengths, they're all in the low or moderate dosage ranges, as I had set this up.

There was no use, as I said, of the long-acting hydrocodone or the hydromorphone. We don't use the abuse-deterrent formulations. It's a red letter day when we see a prescription for a transmucosal fentanyl product. Also for economic reasons, minimal use of the oxymorphone. There are

only 13 prescriptions, and it was more early in the 5-year period because the long acting's been removed from the market. The long acting tramadol, only 40 prescriptions over the 5 years.

What do I think about all this? I admit that we don't often use these high-dose formulations, but for those few patients where we need it, I can't stress to you enough, we are very judicious in our use of the opioids. We're very responsible academic citizens here in recognizing what's at stake.

Hospice has been affected by drug abuse and diversion. I just finished a research project with Dr. John Cagle from my campus, where we see that at least every hospice we surveyed of 400 across the United States had at least one confirmed case of opioid misuse, abuse, or diversion in the previous 3 months. And 80 percent of the time it's a family member, not the patient.

So we're very mindful of that. But I am concerned that if we remove these high-dose formulations, this would cause a hardship for these

patients; for one thing, the tablet burden. If you remove the 80-milligram oxycodone, while we don't use that very often, you could say, sure, just take double the number of 40s, but if you've only got 2 or 3 good swallows in you a day, you just doubled that, and you've doubled the number of tablets in circulation, and in the home, which is a big concern for me.

Also, there is the financial implication here. Often, we see that the pharmaceutical industry will charge the same amount of money for the same number of tablets regardless of the strength. If you say take 2 of the 40s instead of 1 of the 80s, you've just doubled the cost. Either the patient is paying for that, or their insurance company if they're under palliative care, or if it's hospice, the hospice program is providing that.

Also, some pharmacy benefits managers with the Q12 hour drug will only allow 60 tablets a month, so what's the patient going to do when they need that other half? Our options are limited for

these patients who have legitimate pain. I worry what would be their fate, and I'm not convinced that making these very few patients pay this price would have an enormous impact on the opioid crisis. But again, I'm very sensitive to all sides of this issue.

I'd like to thank Brie Noble, who kept me going from completely blind with this data set by helping me to manipulate it. Thank you very much.

DR. HERNANDEZ-DIAZ: Thank you very much.

We will now continue with another invited guest speaker presentation, with Ms. Marianne Farrell.

Guest Speaker Presentation - Marianne Farrell

MS. FARRELL: Hello. Good morning. I have no slides. I'm just going to present my story. I am Marianne Farrell. I am from Pittsburgh, where I facilitate the chronic pain support group. I am affiliated with the American Chronic Pain Association. Just a little bit about myself, I have been married for almost 51 years. I have 2 adult children and 5 wonderful grandchildren.

My story starts in 1984 going to a doctor's appointment. I was driving down the road, a two-lane road. I'm coming to an intersection. I see a car. I kept driving. All of a sudden, boom. I'm hit, broadsided. I just remember holding on to the steering wheel, I'm moving back and forth, and all of a sudden, hit again.

I looked down. I was still alive. I thought I was going to die, but I didn't. I got out of the car, nothing, no blood, no broken bones. I thought this is my lucky day. And I guess it was, until the next morning when I woke up. My lower back started hurting, my right leg, and it's never stopped.

That was 34 years ago, and now I'm 72. So about half of my life I have lived in constant pain. I use the term "constant pain" because chronic is thrown around a lot. Some people say I have a chronic cough. I have chronic foot pain. But when you tell people constant pain, some of you maybe don't know people like me. I don't get a day off. I don't get a month off or a week. I don't

get an hour off. The last thing before I go to sleep is pain. The first thing I feel before I even wake up and open my eyes is pain.

Why am I telling you all this? I went to so many doctors, well-meaning people, wonderful people who tried to help me. My pain kept getting worse and worse. I looked fine. I had to take a leave of absence. I am an elementary school music educator. I taught the little children dancing and singing. I loved what I did.

I had to take leaves of absence from that, of course. The pain got worse every day. The doctors gave me all kinds of different opioids. Either I had severe side effects from them. Once I was given I think it was codeine, and I felt my throat closing and had to be rushed to the emergency room. That happened twice to me.

I'd try anything that the doctors asked me to do: acupuncture, chiropractic, massage, you name it. I took it and tried it. Nothing worked. So I was on different things like tramadol, if that's what it's called, and Ultram, and things

like that. It didn't touch the pain.

So then I was sent to a pain clinic, and I was happy to go. I thought, wonderful, this is going to be good. The first thing they wanted to do with me is giving me spinal nerve injections and nerve blocks, so I did it. Nothing worked. It didn't work. It didn't touch the pain. I kept going. I did anything they wanted me to do.

Finally, this pain specialist said to me, "Marianne, we're going to do something. I think you're a candidate for a rhizotomy." I didn't even know what that was, and I thought, "Okay, rhizotomy." They did it. Nothing. No pain relief. Then I had a doctor that said -- oh, I'm still at the pain clinic, and he said, "We're going to give you methadone." I thought, "Okay, methadone. I'd heard of methadone." I tried the methadone.

A couple of weeks, it was great. I was doing real well, except one day I was crossing my living room. I lost all bladder control. It was horrifying. And my husband said to me, "Oh, maybe

you're just getting sick, or a bladder infection, or whatever." So I kept taking the medicine. It kept happening and happening. I couldn't leave my house.

I phoned the doctor and I said, "Something's very wrong. It has to be this medicine." "No, Mrs. Farrell," he says. "You're on a low dose. Methadone would never do that to you." Ha! Well, here I am. So he said, "You stay on it." So he didn't believe me.

I went to the psychologist I was seeing for depression. Show me a person with chronic pain, and I'll show you a person with depression. It could be high, it could be low, but it's there. So I went to the psychologist and I started crying uncontrollably. I kept saying, "What am I going to do? He tells me to take this medicine. I can't take this medicine. The pain is unbearable." I stopped it. I just couldn't stand it. The psychologist said, "Marianne, would you let us put you in the hospital to see if we can help you?" I said, "Sure. Put me in."

My husband text me, and he said, "Marianne, we should go right from here. We're going to go into the hospital." So we did. I'm walking down the hospital hallway, here's a door, so we had to ring a bell. I'm thinking, "Oh, this is strange." A nurse comes and opens the door, takes me in, and I hear people screaming. I'm hearing all kinds of noises. And he's holding my hand. I'm crying. I'm saying, "What is this? Where am I?" He's crying. And he said, "Marianne, please, just stay here. We don't know what to do with you. Just stay here. They're going to help you here."

Of course, it was a psychiatric ward, and I was suicidal by this point. So I went in, and every hour, somebody would knock on my door and come in and look at me and say, "Oh, we're just checking. We're just checking on you." And I'm saying, "Ugh."

Finally, that evening, the pain doctor from the hospital -- this is a small regional hospital. This was not in Pittsburgh because we lived outside of Pittsburgh for a while. This doctor comes in

and says, "Marianne, I know you've been going through a terrible time. I'm going to help you. I'm going to give you a patch to wear. It's going to help." "Great. Do it."

He puts it on me. I was scared to death, though, because of all the terrible side effects and things that had happened to me. He puts this patch on, and it's time to go to bed high. I thought, "If this patch -- I have a terrible side effect. If I can't breathe, I don't care anymore." So I went to sleep. I woke up the next morning; oh my God, it was a miracle. I had no pain. I thought, "Oh, I don't know what this is, but I want it."

The doctor comes in the next day and said, "How do you feel?" And I said, "This is great. What is this?" He said, "That's a fentanyl patch." Nobody ever tried that before on me. I thought, "This is good." I had to stay in the hospital for 2 weeks and had all kinds of other group therapy, whatever. I didn't care. I got this patch and went home.

A couple months went by. I kept checking in with the doctor. A couple of months went by. All of a sudden my hair starts to fall out and I lost my appetite; didn't even want to look at food. My husband and my family are all worried about me. I said, "I don't know. I just can't eat." This is something strange and everything. So I called the doctor, and he said, "We have to take you off the fentanyl. It's too strong for you." Well, he might as well have said we have to cut your head off because I'm so upset, but I knew I couldn't stay on it.

He said, "I'm going on vacation, but I'm going to call you in a prescription that will help you get off of fentanyl." I said okay. The next day we go to the drugstore; he forgot to send in the medication to get me off of fentanyl. So I went through narcotic withdrawal 4 or 5 days. I guess I should've gone to the emergency room. I'm not a medical person. What do I know? It was a horrible experience.

I have fibromyalgia. I have 2 herniated

discs. I have TMJ, and because I've had 3 bouts of shingles, I have some postherpetic neuropathy. I'm not telling you all this for sympathy or empathy; it's just a fact of my life.

What was I saying here? After I went off the fentanyl, I didn't know what to do. So I got over the withdrawal. For 23 years, out of the 34 -- I saw a term up here "under-medicated" or some kind of pain where you're not getting enough medicine to help the pain. That was me; not 23 days, 23 months, 23 years; not anybody's fault. They all tried. I tried.

Finally, here's where the good part of the story comes in. Eleven years ago, my doctor said to me, "Marianne, there's a new kind of opioid I want you to try." "Sure. I'll do anything." She gave it to me. I took it, and within a day, I had wonderful relief. It didn't take it all away by any means but substantial. I could drive the car a little bit again. I'd been playing the piano since I was 5 years old. I could actually sit down and play the piano a little bit.

So my life changed. This opioid medication gave me hope. It gave me a cause to live, to function, to enjoy my family, to enjoy my grandchildren, and that's all I needed. That's all I wanted. So do I have concerns about being on opioids long term? No. Hell, no. I'm 72 years old. If it takes a year or two off my life, I don't really care. I mean, I care, but I care more about functioning and being a functioning happy person.

Do I worry about my kidneys or do I worry about my liver? No. I just can't worry about it. If you talk to a person who's had long-term pain like I have, I think everybody would tell you, I can live again. I'm not suicidal. I was suicidal at least 2 or 3 times, and my husband just begged me, for the sake of our children, don't take that bottle of pills, please, so I didn't.

Do I have nausea? Do I have dizziness? No. Do I have constipation? Hey, that's a small price to pay if it helps the pain. Do I worry about falling or balance? I could fall because I'm 72

years old, let alone because I'm on opioids.

I just wanted to say before I close, because I am a facilitator of a chronic pain support group, I'd like to just say I'm not just here telling my story. I have two people in my group that I just want to relate a little piece of what their life is like.

A man named Jeff, who's 61, had several back surgeries; terrible, a lot of nerve injections, spinal nerve injections. Anyway, this condition has left him with something -- I don't know whether I'm saying it right, arachnoiditis, something to those terms. He suffers terrible pain.

I asked him, I said, "Jeff, if your doctor said are you going to stay on these, would you continue taking these opioids?" He said yes. He said, "Because I hurt a lot even taking them. If I want any kind of a life, I will remain on them the rest of my life."

Real fast, the second woman I'm talking about is a registered nurse. Her name is Ashley. She's 31 years old. She's had chronic pain for

4 years. She was hurt at work. They took her to the emergency room. Being a nurse, she knew the severity. She said, "Please, please. I need an MRI." "Oh no --" this is another little regional hospital -- "Oh no. We don't send people for MRIs from the emergency room. You'll have to see your doctor the next day. Here, take these muscle relaxants and go home," and she did.

Woke up the next morning, she could hardly move. They get her back in the emergency room, and then they decided to do an MRI. It turns out she has cauda equina syndrome; horrible, horrible pain; told her she'd never get pregnant, and she's on heavy dose opioids.

In the beginning, they wouldn't even give her any. They said, "You're too young. We can't give you opioids. You're 29 years old," but they did. Anyway, they said she will never get pregnant. And guess what? She is. It's a miracle how she's going to carry this baby and have this baby. It's the joy of her life. Somehow -- she told me, she said, "I'm off everything now,

Marianne, but as soon as this baby's born, I'll be back on my opioid analgesics."

That's really all I have to say, except I know about the opioid crisis. We hear about it every day. I know an acquaintance of mine who's lost her daughter because of an opioid overdose. It's tragic. I feel for them. I see them. But there are always going to be, remember, people like me for whom nothing else works for our life, so that we can live it and want to live it. Our families are so affected by chronic pain. It's not just me, the person. Our families are so affected.

So there will always be a need for it. I know the opioid crisis, but here's my last thing here. We, people with chronic pain, we are having our own opioid crisis because doctors are refusing to give them to people like me. They want to titrate them down. I hear all of these things. I see what you're saying. I believe you. But there will always be a need for people like me to have them in their life, and I thank you.

DR. HERNANDEZ-DIAZ: Thank you so much,

Ms. Farrell.

We will now continue with another invited guest speaker presentation with Mr. Andrew Kiezulas.

Guest Speaker Presentation - Andrew Kiezulas

MR. KIEZULAS: Good still morning, everyone. Before I begin, just a brief disclaimer. I have nothing to disclose. I should have probably added that I'm taking off of work to be here, so technically I'm kind of paying to come speak to you, so take everything I say with a grain of salt. I'll start with that.

There's something I definitely want to do before getting into some of the bulk of the presentation, and that is to give a few shout outs. First and foremost, to the other volunteers who are here.

Doctor, you showed up years ago. You cared about this issue. It moved you, and you showed up, and you participated. You're now here in a different capacity with a different message. You're still here, and that really matters. There

are a lot of people who feel like they should not be part of this process. They're disenfranchised and don't feel like they can have an impact with this; while I'm here to thank all the people who have showed up and who do care enough to be a part of this process, so thank you very much.

Fellows in recovery, I want to say thank you. You inspire me. You help keep me sober, and that is a huge part of my program, is the gratitude. A friend of mine, 20 years sober, a mentor, said, "Stay grateful. Watch things continue to stay good and get better." So gratitude, gratitude, gratitude. Thank you. We can and do recover. We can and do recover.

To the families and friends that are in the audience, again, gratitude. This issue does affect more than just people with chronic pain or people taking these medications. This has a very real and tangible ripple effect. So to the families and friends that have shown up here, respect.

The professionals, many of you are here because it is your work. I have a feeling you

didn't get into this work by accident. Many of you have a story of your own, and I wanted to thank you for really dedicating your lives to doing research and helping to equip people for more educated solutions to these issues, and I'll move on from that.

The FDA, obviously, many thanks for having us. In short, you could have chalked a lot of the negative externalities of prescription medications to bad decisions, bad people making bad choices or they had bad parents. We know that not to be the case. You've done your homework.

The surgeon general actually came out recently, I was just reading today, about his brother, who is currently incarcerated, asking to be transferred into treatment. That's a whole 'nother story. But two parents who raised the surgeon general also have someone in their family with a substance-use disorder. So it's not just about parenting, and it's not just about the students. There's more going on, a lot of biopsychosocial, and we have a lot of researchers

here that can talk way, way better about that than I can.

But again, thank you. The truth fears no question. The only thing that the truth demands of us is to change our minds if the truth comes up. So I dare all of you to keep asking yourself what is the truth? What is the current truth? How can we find solutions to this right now and where are we at?

A brief introduction. This is my niece Jillian [ph], trying to squeeze the life out of my face. My name is Andrew Kiezulas, and I'm a person in long-term recovery. For me, what that means first and foremost is that Ma has her son back, but also Jillian has her uncle back. And I'm really, really proud to be able to stand here and say that.

Our family continues to heal. And where you have recovering people, you have recovering families, and you have recovering communities. I would love to see the voice of recovery elevated, and celebrated, and becoming the norm. And it is becoming more and more the norm, but it still has

yet to I think break that ceiling and become like a mainstream part of conversation.

Jillian. We joke. She's 9 years old, and we joke that she has more sober time than her father and I. I just celebrated 7 years this May 3rd. Thank you. I'm not saying that to celebrate myself, but to show that it's possible. And I'll get into some of the reasons why and why that should be kind of focused on for a minute.

We have an open dialogue with her. Her father is also in recovery, and we have an open dialogue with her about why we used, some of the things that led up to it, and just the running conversation about where everyone's at. So if something does happen, genetics, mentally, emotionally, biochemically, something happens to her in the future, we have some momentum towards recovery-based principles.

I'm also a two-time graduate of the University of Southern Maine. My undergrad's in chemistry, and I went on to get a master's. I had a mid-college career crisis and decided, you know

what, I don't know if industry's for me, chemistry. Maybe I'll go into policy. Policy's a tough road. Again, my hat is off to all the policy advocates in the room; recovery policy, even tougher.

But I decided to go into industry after I secured the masters. So I'm actually a chemist, which it still makes me laugh. It also makes me almost cry because it's a dream that I completely gave up on a very, very long time ago. I thought it was someone else's reality to pursue. I would never be able to get there with my injuries, with my emotional state, and my mental state. I definitely degraded very quickly.

I'm also the co-founder of the Recovery Oriented Campus Center, the Rock, at USM. It's a collegiate recovery community right on campus, a meeting place for students who are seeking recovery or recovery allies. I'd like that term to be elevated.

I know this is a very different presentation than the others. But I would love to empower all of you to feel able to seize upon the identity of

recovery allies and recovery allyship. A lot of us here know someone who may be in active use or in recovery. You support them; you're a recovery ally. Please celebrate that.

I'm also one of the founders of YPR Maine, Young people in Recovery. If you have not heard of YPR, I'd love for you to check them out and on your own time. They do a lot in the recovery policy and recovery advocacy world, locally, nationally, and statewide.

At this point in the presentation and right before lunch, I'm sure some of you are very hungry, I often hear when we do work in the community with professionals in, and mostly law enforcement, "Andrew, none of us have ever had a use disorder, and we don't know what that is. We don't know what you're talking about." I struggle to take my life experience, my lived experience, and put it in someone's brain to help them really understand.

One day, this was in recovery, it was recommended that I work on my mental, physical, emotional, and spiritual health, and part of that

is diet and exercise. I was meal prepping because fitness is great, and it's all the buzz. I went to school. I was in a rush one day, life happens -- life's a four-letter word -- and I forgot my lunch. So I said to myself, there's a little pizza shop right next door to campus, and I'm just going to run over there and grab a grilled chicken Caesar salad because of fitness, and because of diet and exercise, and because of the mental, physical, emotional, and spiritual health.

As I approached, in my head I'm going, "Grilled chicken Caesar, grilled chicken Caesar." As I approached, I get physically accosted by the intoxicating scent -- and I use that word very deliberately -- the intoxicating scent of pizza and fried goods. And I was like, "Ugh," but with grilled chicken Caesar because of health and fitness. And I got this. I'm cool. I can do this.

I get in line, and I'm standing there waiting for like maybe -- it felt like an eternity, but it may have been like 3 to 4 minutes. All the

while, sitting right in front of me is that glowing case of warmth and comfort in the case. It could be 100 degrees outside, 200 degrees outside, and you want to just snuggle up under that heat lamp because it looks so warm and inviting. And right under it with that golden glow is that pepperoni pizza, and it's just staring you in the face. It's just staring you in the face.

So I get up to the counter, and I'm so confident in my recovery, and I'm doing all these principles, and I get a grilled chicken Caesar salad, and right at the last second, I'm like, "And I want a piece of pizza while I wait for the grilled chicken Caesar salad."

That's a funny story. That's a fun story, right? But that was lunch one random Tuesday. It's funny. I've told the story a bunch of times. And I say Tuesday, and it just so happens that today is Tuesday, and it's about lunch time. I don't share that because I want everybody to be looking and judging each other while they're getting lunch, but this is something to think

about.

If you say to yourself, I can't understand addiction, I can't understand use disorders, well, you very most certainly can. But drawing those threads to other parts of your life is often something you don't have to think about. And God bless you because I wish I didn't have to think about those things, but I do, and this is a constant maintenance thing, constant maintenance.

Just a little glimpse into the recovery world. I was born in Concord, Mass. For the history buffs, Concord, Mass is the birthplace of this great nation, the United States of America. I've actually fished the Old North Bridge from a boat, caught some fish, which is a pretty cool experience in the Concord River. Old North Bridge is where the first shots of aggression were fired in the Revolutionary War.

It's a wealthy area. It definitely has a lot of issues that are covered up because of that wealth. One question I do have consistently is do these studies include private data? If anybody

knows the answer or if anybody has studies that include private data, I'd be curious to see how they compare.

More to the point this word "trauma," how many of these studies are looking through the lens of traumatic experience? I specifically bring up adverse childhood experiences. Kaiser Permanente, thank you for the work you've been doing for decades now. I know we're not really here to make direct recommendations, but what would it take to get some kind of anonymous ACEs screening given to patients who are receiving opioids?

This is not something that doctor will see and then say, "Oh, you can't get them," but this is something to say, "Here's these things --" and it's a questionnaire. It can take 10 minutes at most. "Here's these things that could predispose you emotionally and mentally, not just biochemically, to a use disorder."

There's lots and lots of data, correlation and causation, between trauma, PTSD, and use disorders. That's one of the things that I've

really, really found where I grew up, was just in our tight little community of 5,000 people right next-door in Carlisle, there were three friends, including myself, that were sexually abused as kids.

That's something that I see a lot in the recovery community. Sexual abuse is very rampant, but it's one of those things that if you speak up about, that person has a family, that person has a job, that person has a life, and you're going to ruin their life if you accuse them of something. The abuser becomes the abused. Suddenly, the victim becomes the tyrant.

We're not here to talk about that, but you see these same kinds of things stretching over into other systems, doctors' prescribing practices. I have had a very different experience, and I've been wondering why I'm even here because of the gross overwhelming evidence to keep opioids.

There are a lot of studies and research and testimonies. I had a wildly different experience, and I know a lot of people who've had a wildly

different experience. In fact, the whole just say no thing, I've had friends in recovery who get hurt, go to the emergency room, and say, "No, no. I had an issue. I've been sober so long. I don't want opiates." And the doctors tuck them into their discharge paperwork. And these are people who are now dead, by the way, who have overdosed, friends of mine.

So I'm not here to set up a polar opposite, but an anchor. Let's please do this with discretion. There are recommendations that can be made. I too often hear from FDA affiliates or officials, that's not our job. Well then, please ask yourself, what is your job? Because there are recommendations that you can make, and labels that you can make, and guidelines that you can set up.

That aside, that was my -- I was going to say shot across the bow, but that was more of a -- so that's it for me with the shots. Thank you.

In short, I think this picture really well represents my experience with opioid-use disorder.

In 2007, I slipped on some ice, hurt my back. Now, I did had some trauma prior that predisposed me. I did drink, but I was kind of one of those kids that managed. I went to school. I got jobs. I had bad relationships like everyone else.

But it wasn't until I had access to opiates that they really took hold of me, not just physically. I hear this actually in all the other stories that I've heard today, in the studies, is that it doesn't just treat the physical pain, and that's one of the things that's not made clear. It treats the emotional pain. It treats the mental pain, the depression, and it treats that existential pain.

I actually felt connected to, finally, ironically, a community where people were doing crime, and I did crime to support my habit. I was brought up very quickly on a high dose and I just kicked off as quickly as I got started, and ramped up to 180 mLs a day. I was just discharged.

I don't know how long it takes to develop a physical dependency, because I hear words like

"tolerance." Dr. Row -- excuse me, Michael, I hear words like "tolerance." Is that an equivalent to dependence? And we've heard other terms. There's just a lot of vagueness. There's so much vagueness.

Not to single you out, and I apologize. But I was brought up very quickly. Then as we've heard today -- I was cut off -- in the presentations, and I did go to the street. And then I did certain things to support my habit, and those snowballed the depression, and snowballed the anxiety and the pain, and everything else that goes with that.

I was watching friends die, friends overdose, people, relationships crumbling all around me. And the things that I've been able to hold together, they all started falling apart. But there was one thing that I knew would make me feel better regardless, and that was opioids. So I found it. I found that security.

When I see the differentiation of pain patients and quote, "addicts" -- because people say, "I'm a pain patient. I'm not an addict." And

that word is so loaded. Abuser, that word is so loaded. Language matters. But when I see the differentiation of those two things, what are the commonalities? They want security. They want their lives back. Actually, when people are using, that's what they get for a minute. They get relief.

So maybe I'm here to anchor it with like, hey, yes, opiates are necessary, but let's do it with discretion. What are some of the other things that we can promote? The wraparound services.

I have a horribly bad back, two back surgeries. I spent almost four years on disability, and I had multiple hernias in both discs, still, sciatic, down both legs; pain, numbness, tingling, burning, all that stuff; arms, neck, legs, back; awful.

Naproxen on occasion. I got a Tempur-Pedic bed. That's probably one of the best investments I ever damn made; not to promote Tempur-Pedic. I meditate daily. I stretch regularly. I do yoga, 3-5 times a week. These things so far have helped

me manage.

Again, I would just like to anchor. There are other things that are available that cost, unfortunately, one could argue more money. But in the long run, it will be far cheaper. It will be far cheaper. And this is not to say people who are on opiates should be pulled off of them because I have literally lived the fallout of that. It's terrible. It's horrible.

Detox, oh boy. I've had this feeling. I can still feel it on occasion, and it's bugs, bugs just burrowing their way all over my body, all over my body. Every fiber in me was just screaming, Ahh! Every muscle was tearing from every bone. Every tendon was going, bing, bing bing, just over and over again. That's what detox feels like.

So Marianne, I am so sorry that you ever had to feel that way, but I can relate. There are so many commonalities. There are so many things we can relate on. And really what it comes down to is what would someone choose at that point? You're dying of thirst. What would you choose?

Obviously, you'd choose opiates. You choose the thing you know works.

I'm definitely rambling on.

DR. HERNANDEZ-DIAZ: I have to ask you for the last comments.

MR. KIEZULAS: Yes, okay.

So I do want to say this, not to confuse correlation with causation, nor to blanket statement my story over all other people's stories, but I hear the same thing over and over again, in the recovery community, and from friends, and friends of friends, and my parents, and my parents' friends, lawmakers, law enforcers, policy makers, policy enforcers, across the board, the same story, the same story over and over.

Still, there are a lot of doctors in this room who are ethical, and moral, and doing the right thing. They're just as many that are not. I would love to sit here and say that all this is what is represented out there. It's not. Let's be very careful. Something is clearly wrong with prescription labeling, prescribing practices, and

prescribing policies.

Just briefly, Eight Dimensions of Wellness, I love to see this picture; kind of blasting through this. I don't have the answer to all the questions, and I'm not here to present myself as such. But I do know that I'm here carrying the weight of and sitting very, very heavy with the stories of my friends that were overprescribed, only they do not get to come tell their story, as Marianne said. And they don't get to sit in a room and share their story even there.

They're gone. Their parents will never again hold their child or vice versa. Their children will never again get to hug their parents. This is claiming lives. There is a real, real tangible side effect to this. And by now, we have almost surely, almost all of us, lost someone that we know. If you have not, I would love to live and hope we can one day live in a world like yours.

Some of these people that we lost are complete strangers, but so many of them are families, friends, and neighbors. And really at

the end of the day -- and I'll close with this -- I've been sent here, not by you but by them. And we are left here to share their stories and keep them alive. So with that, I would implore you to do them justice, responsibly. And that's not to take anything away from anyone in particular in the crowd. So I'm done. Thank you.

Clarifying Questions

DR. HERNANDEZ-DIAZ: Thank you.

Are there any clarifying questions for the invited speakers? If you could please direct questions to a specific presenter, and do not forget to state your name.

Dr. Litman?

DR. LITMAN: This is Ron Litman. This question is for Dr. Markman, or actually any of the panelists. There was an article published this week in the New England Journal about this very subject. It just came out the other day, so many of us may not have had a chance to read it. But one sentence in there struck me in particular, and I'll read it.

"An underappreciated challenge with respect to such patients," meaning chronic pain patients on opioids, "particularly those receiving high doses, is ascertaining the extent to which the perceived benefits represent a genuinely salutary effect of opioids rather than the desire to avoid opioid withdrawal, which itself can produce pain and functional impairment."

There is no question. All of us, when we think about these issues, have this in the back of our minds. I was just wondering if you could comment on that, and also any of the other panelists, even Marianne. How do you sort this out?

DR. HERNANDEZ-DIAZ: We have this time for clarifying questions for the presentations, but we will have time for discussion later on. If you have any specific questions for them from the presentations, you can --

DR. LITMAN: Okay. I misunderstood. That's probably not really a clarifying question.

DR. HERNANDEZ-DIAZ: But hold it because we

can go back.

DR. LITMAN: Thanks.

DR. HERNANDEZ-DIAZ: So please, only clarifying questions for the presentations. Dr. Urman?

DR. URMAN: That's me. It's for Dr. McPherson. Regarding your presentation on hospice patients, especially the subset of patients who are getting higher dose opioids, the prescription patterns, based on your research or the data that you looked at, are they limited to just a few prescribers or is it more widespread?

DR. McPHERSON: No, the data was from 19 states. It was from across the United States, very widespread.

DR. URMAN: Thank you.

DR. HERNANDEZ-DIAZ: Dr. Jowza?

DR. JOWZA: Hi. Maryam Jowza. This is a question for Michael Rowbotham. Some of the data that you had shown seems to imply that with respect to tolerance and your thoughts -- at least your data on opioid-induced hyperalgesia, that the dose

escalation that we see with chronic opioid use, is it in your opinion that it's related more to tolerance than anything else?

DR. ROWBOTHAM: What I was trying to imply was that opioid-induced hyperalgesia is a construct for which there are animal protocols to demonstrate it, and there's some data suggesting that it's actually through non-opioid mechanisms.

It gets to the question that was just brought up about is it withdrawal that drives patients to continue to use opioids; that every time they feel the dose wear off, that's the signal that they need to keep taking it. That would not be opioid-induced hyperalgesia. That would be physical dependence, wearing off of the analgesic effects of the opioids.

The purpose of the study was to try and look and see if there was sensitization of the nervous system that would develop over time that would be demonstrable in this experimental pain model, to try and separate that out from this process of opioid effect, and then loss of effect with

increase in pain during that time period, which would really just be opioid effect and then wearing off of the effect, but not something completely different like opioid-induced hyperalgesia.

DR. JOWZA: Thank you.

DR. HERNANDEZ-DIAZ: Dr. Sprintz?

DR. SPRINTZ: Hi. This is Michael Sprintz.

Dr. Markman, I had a question. When you're describing your first patient, you had mentioned that he was stable on buprenorphine for his pain, and then when he had a compression fracture, he had an epidural steroid injection, which I can understand why that wouldn't help him.

One of the things that I noticed is that in some of the discussions, there wasn't talk of other types of interventional therapies. In this case, was kyphoplasty considered to fix the compression fracture, and then just keep him on bup instead of the transition to all these different opioids? I know he's just one example, but the interventional part is part of the treatments, too.

DR. MARKMAN: Sure, that's a great question.

Just to clarify, he was not administered an epidural steroid injection. He did not receive it because of the concern about the cumulative steroid exposure. With respect to kyphoplasty or vertebroplasty, he's actually scheduled for that. He's had a lot of trouble with his counts, so it's been a challenge to do an instrumented procedure with him at certain times because he's had a lot of instability in his counts in the recent period. So that's why he didn't get it up front.

DR. SPRINTZ: Thank you.

DR. HERNANDEZ-DIAZ: Mr. O'Brien?

MR. O'BRIEN: Thank you. Yes, my question is for Dr. Rowbotham regarding two slides, slide 6 and slide 7 -- actually slide 20. The question is, it had come up that you had said that stigma -- if you go to slide 6, please, first -- that stigma and fear of addiction leads to the patient self-tapering and not telling the physician or whatever because they want to come off. They want to try to get off and be normal, and they want to get off of it. Yet, in slide 20, you had indicated

that when it comes to tapering though, that's a very painful process for the patient. On the second line there, it's very difficult to stop that.

I'm just questioning from my own experience and with the patients that we have, clearly, they want to come off because they want to see how normal they can be. And they almost prefer to have a combination of smaller dosage so they can do that in increments, and not have large increment change to see how much pain they're actually in and what they can tolerate, because they don't want to get to 100 percent, but they want to get to something.

But the question is, the experience that you've had in terms of that discomfort with going into a, quote, "official tapering" is because they're not in control of that now? That's what I found in the experience, is that now they're afraid of the physician being in control and going beyond what they're capable of doing.

DR. ROWBOTHAM: Thank you for the question. The hard part for patients is when they feel

they're forced into a taper, like their physician is going to stop prescribing and they're put on a very short taper, that's obviously extremely uncomfortable, and they have no control over it. If patients want to taper -- and it's a discussion I have frequently with my patients, it's a negotiation.

You talk about what might be a tolerable rate. If they're on a high dosage strength formulation, you have to change it so that they can go down in small increments, and you negotiate and come to agreement on some targets. And it's generally a very slow process. That's part of the negotiation. Do you want to come down by 50 percent? Do you want to go off altogether? Over what time period would you like to accomplish this?

I think it's best to keep the patient really in control because usually they'll get to some point where they find that it's just too hard for them to go any further, and that now they're new stable dose. So the best is when it's voluntary and when the patient is kept in control of the

process as much as possible.

DR. HERNANDEZ-DIAZ: Dr. Mackey?

DR. MACKEY: Don't sit down, Mike.

DR. ROWBOTHAM: Okay.

DR. MACKEY: To Mike Rowbotham, first of all, thank you for taking on this issue of opioid-induced hyperalgesia, which is confounded all of us. Three out of 17 people you think may have had some evidence of opioid-induced hyperalgesia. Recognizing you're not dealing with group means anymore, you're taking that subset out, can you disentangle the notion of is it opioid-induced hyperalgesia versus those three just happen to have natural variation of their pain and were doing worse during that period of time?

DR. ROWBOTHAM: We tried to separate out the clinical deterioration part, where despite continuing on a stable dose, their pain scores were actually going up every week. We chose patients that didn't have progressive underlying disease or some other explanation for why their pain might get worse.

The experimental pain model part, just like in the study done by Larry Chu and other people at Stanford, they were looking, again, for whether or not there was a reset of the nervous system sensitivity. They used a heat stimulus. It's a single painfulness of heat stimulus rather than a full hyperalgesia model, and then they used what's called a pressor test, which is this ice water immersion. They had a 1-month exposure at a lower dose of opioids on average. At the maximum, it was 120 morphine equivalents a day in their study, and it was only 30 days of therapy.

We had 6 months and patients being able to go up to very high doses. So we thought if hyperalgesia was a common phenomenon, we might be able to detect it. But again, it was clinical deterioration, and then inferring opioid-induced hyperalgesia by this resetting of the nervous system sensitivity to developing hyperalgesia from heat, and just heat sensitivity in general.

Part of the reason to do the study was it was a term, opioid-induced hyperalgesia that was

just thrown around so much in the press and in the literature, but without much data. There's no working definition of when -- we were trying to inch towards the working definition. It's really going to take more studies and some kind of structured way of looking at patients out in practice because it's just too difficult to do a prospective controlled study to search for it.

Perhaps that's something that can be done in a future study, to figure out, really, what it is, and how do we want to define it. And then once there's a definition, set some criteria for how to detect it as patients are put on opioids, and then maintained on opioids for their pain.

Does that answer it?

DR. MACKEY: Yes.

DR. HERNANDEZ-DIAZ: Thank you.

Dr. Higgins?

DR. HIGGINS: Forgive me if this is not clarifying enough. I'm wondering if Dr. McPherson could let us know if there were any kind of state-by-state comparisons made with the data that

she's collected. It's a fascinating sample, and I'm just wondering if there are things that affect the rate -- or patterns of types and rates of prescriptions across states. I'm thinking if the drug monitoring program lacking in Missouri as well.

DR. McPHERSON: I did not attempt to do a state-by-state analysis. Certainly, we could consider doing that, but we did that. But I'd like to run it again. And the next thing I'd like to look at, too, as we saw from one of the FDA people, is looking at is there a decrease in prescribing, because I do believe this is happening in hospice, so I'd like to look at that, too.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Becker?

DR. BECKER: Yes. Will Becker. A question for Dr. Markman. I'm just curious about the use of buprenorphine in the cases you mentioned. Was that under an X waiver, and what formulations did you use? And full disclosure, I use off-label buprenorphine for transitioning folks off of high-dose full agonists.

DR. MARKMAN: I think there is a lot of uncertainty -- a great question, first of all. There is a lot of uncertainty about what the extent of comorbid expression of opioid-use disorder and chronic pain is in the population a lot of us take care of, so that's always complicated to sort out. We tend to go through the checklist, which I put up very quickly, and talk about patients; go through them in a very itemized way to identify whether they have features of mild, moderate, or severe opioid-use disorder; whether they have episodes of withdrawal, which I believe was asked about.

Then we try to answer their broader overarching question, which I think is the most compelling one, which is do you feel like it's out of control for you? I think in most cases, if that's the case, then we will use X waiver, and we will prescribe using the X waiver. We'll use it at the 2-milligram formulation or the 8-milligram formulation. We'll induce them in the office.

I think to the point that Dr. Rowbotham was making, we have found this to be an incredibly

powerful tool to address the challenge which he identified, which is it's very hard to begin that negotiation to begin an opioid taper. But with buprenorphine, you can compress what might take 6 months into 16 hours. I think that you can always go back if you can't tolerate because you're too nauseated or whatever side effects you have. So we have found it to be a very powerful tool to give us flexibility.

Also, if we don't find features of opioid-use disorder, we'll use transdermal buprenorphine. We'll use a buccal buprenorphine. So we'll use the other formulations. The availability of those other formulations has given us more latitude in terms of not having to use the X waiver or right off label, which we greatly appreciate.

Obviously, the one caveat to that, which all of us are aware of, is the cost barrier of using those other formulations. When you use it on label for analgesics, it can be significant, so oftentimes that's an access to care issue, which we

have to negotiate as well. And I hope that answers your question.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Nelson?

DR. NELSON: Thank you. Lewis Nelson. Two questions, if that's possible, first of Dr. Markman. Could you give your perspective, perhaps, on how the incidence or prevalence of chronic pain has changed over your 25-year career, and why, if it has changed, do you think it's changed?

DR. MARKMAN: That's a very interesting question. I think that there has been a change in how we conceptualize what constitutes chronic pain. As you know, there's been a controversy when the number of 100 million Americans experiencing chronic pain was promulgated through the National Institute of Medicine and in our major journals like JAMA.

I know some of the members of this panel, in fact, have been involved with revising those numbers based on how many days of the week, or how many months of the year, or how consistent, or as

we heard earlier, how constant the pain is.

So I do think there's been a changing epidemiology around how we define chronic pain and its impact. We have ranged from 25 million Americans to 100 million Americans when you look at the broad epidemiologic data about impact with regard to severity.

In my own experience, I think we have so many treatments for cancer, as you saw today. We have so many treatments for acute trauma. We have so many ways to stabilize patients and get them through severe illness. And I think our ability to do that has only increased, and patients are, frankly, living longer with more of these cumulative diseases.

What I have seen -- and again, I have a very skewed sample because I'm a sub-specialist. But what I see is our successes in managing acute illness, our successes in treating cancer and other conditions, have led to this population of patients who have an accumulation of disorders, many of which tend to be painful. That's what I have seen.

But again, that's a very skewed, narrow selection.

DR. NELSON: Great. Thank you. If I could just ask Dr. Rowbotham, please, just to clarify, again -- the word "disentangle" is a good one because of the intricacies of tolerance, and dependence, and hyperalgesia. We always think about tolerance is that the effect of the drug wears off, but it could equally be conceptualized as neuroadaptation, and the pain actually worsens to meet the medication that you're perceiving, which in some sense would be hyperalgesia.

So is it possible that when we're looking for hyperalgesia, we're looking for something that's maybe more uncommon or more extreme than just neuroadaptation; and that being an explanation for why the chronic use of opioids ultimately stops working to treat pain?

In other words, tolerance/hyperalgesia or neuroadaptation, and maybe explaining why people who start opioids maybe develop chronic pain, and that being the etiology of chronic pain, being this sort of neuroadaptation/hyperalgesia.

DR. ROWBOTHAM: The way I conceptualize tolerance is that you either have to take more opioid to get the same amount of pain relief, or if the dose is fixed, the pain actually comes back up to where it was before starting opioids. It's hard to keep those two clean in a clinical trial, so the studies that I've done have generally been a titration period and then stable fixed dosing, so that you could see a gradual loss of analgesic effect by the pain scores coming back towards what they were at baseline, like what I showed in the Moulin study.

The hyperalgesia, the testing that we did, just like the Stanford study done by Larry Chu and his group, with the ice water immersion and for us the brief thermal sensitization, it's done in the part of the body that is not painful. We validated it as being opioid responsive by doing studies that I showed in healthy volunteers.

So it's just looking at how sensitive the nervous system is to becoming -- or how easy it is to make the nervous system become sensitized to a

noxious stimulus. The way these pain models work, these hyperalgesia models work, is you provide enough painful stimulus for long enough that you temporarily sensitize spinal cord and brain cells so that you now get an area of hypersensitivity to light touch, or something equivalent to pinprick, in an area around where you delivered the stimulation.

So it's a very artificial construct, but it tells you something about the state of the underlying nervous system. What's still unclear is what is the mechanism of that, and it may be a non-opioid mechanism altogether. But I agree with you in that it's more extreme and it's probably something that develops only in a small subset of patients.

But all patients do develop tolerance and they do develop physical dependence. You can demonstrate that with a single dose of opioid. If you give a patient, let's say, two 6-milligram injections of SubQ morphine, and then you come back 12 or 14 hours later and you give them a small dose

of naloxone, they will experience physical withdrawal.

Opioid dependence starts with the very first dose. Tolerance is something that takes a little longer to really be demonstrable, but it probably also starts with that first dose. Hyperalgesia I'm positing as something of a separate construct. This is probably more for Dr. Mackey to comment on, that's somewhat distinct from the basic process of dependence and tolerance.

DR. HERNANDEZ-DIAZ: Thank you.

Any other questions for Dr. Markman? He will be leaving, so we need to address the questions for him right now.

(No response.)

DR. HERNANDEZ-DIAZ: If not, we will now break for lunch. We will like to meet again in this room in one hour from now, at 1:15. Please take any personal belongings you may want with you at this time.

Committee members, again, please remember that there should be no discussion of the meeting

during lunch among yourselves, with the press, or with any member of the audience. Thank you.

(Whereupon, at 12:14 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:15 p.m.)

DR. HERNANDEZ-DIAZ: Welcome back. We will now proceed with a presentation from invited speaker, Dr. Sandra Comer.

Guest Speaker Presentation - Sandra Comer

DR. COMER: Good afternoon. I'd like to thank the FDA for inviting me here to give this presentation. These are just some of my disclosures. I think part of the reason that we're here is captured in this figure. The number of opioid overdose deaths have increased dramatically over the past couple of decades. There are different kinds of solutions that we need to think about for illicit fentanyl and heroin overdose deaths, but the thing that we're focusing on for this meeting is the deaths due to prescribed opioids. That's shown in the red here.

There have been a number of strategies that have been proposed, including increased focus on developing non-opioid alternatives to treating pain and limiting prescribing of opioid medications. I

think the topic that we're discussing now is one that is an interesting possible solution in terms of limiting the maximum opioid doses that are available. I would like to thank the FDA for taking such a careful approach to thinking about this option because it's possible to have a lot of unintended consequences of making such a move.

I'm going to focus on the role that dose may play in illicit use of opioids. There are four main topics that I want to cover. One is the pharmacology of the opioid, the state of physical dependence of the person who would be using these drugs, their drug use history, and the presence or absence of pain. I'm focusing on these topics because I think it's important to put any discussion about limitations on doses within a framework that I think is something that maybe a lot of people don't think about.

A lot of the studies that I'll be describing to you today were conducted in a laboratory with human research volunteers. Most of the studies that I'll be describing were conducted on an

inpatient basis, so people came into the hospital, and they lived there for several weeks. Most of the studies involved people who were dependent on illicit opioids. They were not seeking treatment for their drug use. Their main motivation for coming and working with us is that they were paid for participating in this study.

The primary dependent measure for these kinds of studies include subjective effects, and one of the primary endpoints that we look at is ratings of whether or not somebody likes the drug effect that they're experiencing. They also answer questions like do you feel high; do you feel a good effect; do you feel a bad effect? So we try to capture a range of different subjective experiences from the drugs that we administer to them.

In my lab in particular, I'm really interested in studying drug-taking behavior because that's the thing that kind of leads to a lot of problems associated with opioid use. We call it drug self-administration. I'll describe to you a little bit the model that I use. But the primary

endpoint for these types of studies includes a progressive ratio breakpoint, and I'll explain what that means in just a minute.

The subjective effects questionnaire looks something like this. They see a label at the top saying I like the drug effect. It most commonly now is on a bipolar scale, so it's disliked very much on the left and liked very much on the right. The person just marks along the line where they feel whether or not they like the drug effect in that moment. The other scales are usually on a unipolar scale, so it goes from not at all to extremely, and again, they just mark how they're feeling at that moment.

The drug self-administration procedure that we use is a drug versus money choice. They experience both reinforcers during a sample session, and then during a later choice session, they can choose to work for either the drug that they sampled or the money. The way they do the work is by making finger presses on a computer mouse, typically, and they have 10 opportunities to

choose between drug and money. Each time they choose drug or money, they're earning a tenth of what they sampled, so a tenth of the dose or $2. We're measuring the amount of responding that's elicited by the drug and preference of the drug over money.

This is kind of what it looks like. Somebody sits in front of a computer. They respond on buttons to choose either drug or money. If the person sampled 50 milligrams of drug, for example, and they choose drug on 7 of the 10 trials, then at the end of the trial, they will have earned 35 milligrams. If they chose money on 6 trials, then they will have earned $6.

This is what we're measuring, is the break point. Each time they choose drug or money, it becomes harder and harder and harder for them to get that fraction of the dose. We're wanting to understand how hard they'll work in order to get the drug or the money, so at the end of the trial, they get the money and they get the drug.

The first study that I'm going to show you

included people who were regular heroin users. I'm showing you the demographic variables just so that you kind of understand the population that we're working with here. They tend to be in their late 30s, early 40s. They're mostly male.

They come from a wide number of ethnic groups. This group was a group of daily heroin users. They preferred using by the intravenous route. They also almost always are cigarette smokers. They use other drugs as well, including cocaine and benzodiazepines, and they drink alcohol.

The first concept that I want to put out there is drug potency. This is showing you ratings of drug liking as a function of dose that we gave. In this particular study, we took the heroin users. We maintained them on morphine during this study so they wouldn't go through withdrawal, and then we started testing the effects of different opioids.

I'm only showing you a fraction of the drugs that we tested just for clarity sake, but basically what you can see is that all of the drugs produce

dose-related increases and ratings of drug liking. We tested fentanyl, heroin, and oxycodone. Fentanyl is obviously more potent than the other drugs, and they liked the effects that they were experiencing.

When we looked at drug self-administration -- again, this is dose along the X-axis, and here is the mean progressive ratio breakpoint value -- the pattern of responding is almost identical to ratings of drug liking. Under these conditions, we consider these drugs to serve as positive reinforcers. They like the effects that they're experiencing. They feel good effects. They feel euphoria, basically, and they self-administer the drugs.

Another concept that I think we need to pay attention to when we're thinking about doses and whether or not we should limit high doses versus low doses is the concept of efficacy. This is data that Sharon Walsh collected a number of years ago to examine the effects of buprenorphine. It's a partial mu opioid agonist and kappa antagonist.

What I'm showing you here are subjective ratings of feeling good effects. Across the range of doses that were tested -- so this is buprenorphine here given sublingually. These were in non-dependent people. Buprenorphine produced a dose-related increase at low doses, but then the effect plateaued, and she's calling this a ceiling effect here; whereas with methadone, there's a dose-related increase. That's an interesting pattern of effects, but one that's common among partial agonists. You often will see this type of responding.

We also did a study where we directly compared the effects of buprenorphine and methadone. We gave both drugs and all of the doses intravenously. In this study, we brought heroin users into the lab. We detoxed them over the course of about a week or so, so they were not physically dependent on opioids. Then we started testing.

These are ratings of good effects. Sharon showed a plateau effect here. We were a little bit

nervous about giving higher doses at this time. This is 8 milligrams given IV, which is a pretty big dose. In hindsight, we probably could have gone higher. You can see that the slope of the dose-response curve is a bit more shallow for buprenorphine than it is for methadone but the effect varies depending on the measure that you were looking at. This is good effect, this is high, and this is how much they would be willing to pay service.

So the slope of the dose-response curve for buprenorphine is a bit more shallow than methadone for dose effects. But for other effects, the slope is almost identical. Here, buprenorphine is looking more like a full agonist: ratings of drug liking, quality of effect, and how potent it is.

The point here is that the effect of this partial agonist may vary depending on the route of administration that it's given under and the effects that are measured. Another really important variable is whether or not the person is physically dependent on opioids.

Here I'm showing you, again -- this is the same data that I just showed you with drug liking for buprenorphine and for methadone. When we looked at self-administration, though -- all of the active doses of drug were self-administered at really high rates. Here's methadone. At a dose that produced a non-significant increase in drug liking -- so the liking was pretty low -- they're still responding quite a bit for that dose of methadone.

My background is in doing preclinical research, and one of the big advantages of working with people is you can ask them why they did what they did, so I did. During a debriefing session, after they completed the study, I just asked, "Why did you respond so much on most of the sessions?" And they said, "Well, some of the doses, I didn't really feel the effects that much, but I slept better that night," or my low back pain was gone.

So these drugs were essentially serving as negative reinforcers. We heard from some of the other speakers that you go through these repeated

cycles of withdrawal during the day, or if you can't get your medication, you go through even more severe withdrawal. We know that drugs function as both positive and negative reinforcers, and that's kind of what was happening here.

That was under non-dependent conditions. In physically dependent people -- again, this is that first study that I showed you. I showed you before the fentanyl and the oxycodone. Here, I'm adding the buprenorphine that we tested. These were in people who were maintained on morphine, so they're physically dependent.

Under these conditions, buprenorphine is producing dose-related increases and ratings of good effects, but it was also the only drug that we tested. We tested 5 drugs in this study, actually. It was fentanyl, buprenorphine, oxycodone, heroin, and morphine. Of all the 5 drugs, buprenorphine was the only one that significantly increased ratings of bad effects. Under these conditions, buprenorphine was precipitating withdrawal. They started feeling sick. They sometimes had to run to

the bathroom and throw up, and it was the only drug that was not self-administered at any of the doses that were tested.

Now, we'll switch gears. Just to sum what I've described to you up till now, potency is an important issue to think about when you're deciding whether or not to limit the doses. Efficacy is a very important thing to pay attention to, and the state of dependence of the person, either the patient or the drug user.

Then there are a whole host of non-pharmacological factors that matter as well. One is drug-use history. This is a study that we conducted on an outpatient basis, where we tested the abuse liability of orally-delivered oxycodone. We looked at people who were healthy volunteers, who were not using illicit drugs at all, and then we also looked at recreational opioid users.

They were matched pretty well on most demographic variables. The healthy users were required to have used opioids medically at least twice in their lifetime, and the others had a

regular recreational use of opioids. This group also had a lot of other drug use.

Here, I'm showing you the strength of drug effects after oxycodone administration in the two groups. The non-abusers are on the left and the abusers are on the right. Sorry about using the word "abuser". At the time, it was okay, but I avoid that term now. Placebo is here. 15 milligrams and 30 milligrams are shown in red and blue.

The thing that was a little bit surprising to us is that ratings of strength of drug effect were not different across the two groups of participants; neither was ratings of good effects, so they were also similar. For this particular endpoint, it was not dose related. Ratings of bad bad effects, however, increased in a dose-related manner.

Thirty milligrams produced increases in bad effect ratings for both groups, and again, nausea and vomiting were common side effects of these opioids, as you would expect. We think that the

increases in ratings of bad effects were suppressing the good effect ratings at the 30-milligram dose.

We also asked them to complete a self-administration paradigm under two conditions. Dr. Rowbotham and mentioned a cold pressor test. We also used that in this study. We had one condition, in blue, where we asked people to experience the effects of oxycodone when they repeatedly had to put their hand in cold water, so that was our pain condition. Another condition was they put their hand in warm water, so it was 37 degrees.

In the non-abusers, they self-administered oxycodone in a dose-related manner under the cold water conditions, so when they were experiencing pain. But when they were in the warm water condition, they didn't self-administer oxycodone hardly at all. In contrast, the illicit opioid users self-administered oxycodone regardless of pain condition.

The presence of pain is obviously a factor

that may contribute to whether or not somebody develops an opioid-use disorder. As you might've read in the briefing book, we don't have really good data showing a strong correlation between the presence of pain and the development of opioid-use disorder. I think some of the other speakers that are coming up will talk about this topic.

I've tried to stick to showing you mostly clinical data, but I'm going to show you one rat study. Colleagues of mine at Columbia, I was getting frustrated because we can't really do this study in people, so I talked to them about doing this type of study in rats. What they did was they took two groups of rats, one that received CFA; it's a complete Freund's adjuvant. It's an injection of a chemical into the hind paw that produces this inflammatory pain that lasts for a while, and then another group received saline.

What I'm showing you here is heroin-induced dopamine release under two dose conditions, 75 micrograms and 150 micrograms. For the saline-treated animals, this dose of heroin, which

is very frequently self-administered, produces this nice, robust increase in dopamine in the nucleus accumbens, which is the area of the brain that's really associated with the abuse liability of a number of different drugs, so that's kind of what you would expect to see.

In the animals who had this pain condition, this dose of heroin did not increase dopamine release. The presence of pain somehow was altering the ability of heroin to increase dopamine. But at the higher dose of heroin that was tested, it did produce this dopamine release. That's kind of interesting to see.

Then, of course, the next question I had was, so what happens with self-administration? Does that mimic the pattern of responding with a dopamine release? And the answer's yes. Again, in red are the animals in pain. At the low dose of heroin, they self-administer less than the control animals. But when we give a really high dose of heroin, then the self-administration goes up dramatically. That has some implications in terms

of thinking about the role of high doses of opioids and their propensity to produce addictive-like behaviors.

Again, these studies were done in rats. We need to try to replicate them in humans. It's challenging to think of a design that we could do that would be ethical. I talked to my PET imaging colleagues at Columbia to see if we could try to capture opioid-induced dopamine release in patients with pain and those without. Unfortunately, the amount of dopamine that's released by opioids is really small and hard to measure in people. So, I don't know. Hopefully someday, we'll have a tool that we can use to mimic the rat data.

Just to summarize, under most conditions, higher opioid doses produce greater positives, subjective, and reinforcing effects. Things to think about when we're deciding whether or not to limit high-dose availability include potency and efficacy; route of drug administration is another factor that is important; state of dependence; and drug use history in the presence of pain.

There are also other factors that I didn't go into, including genetics, the sex of the person and environmental factors. I think somebody else talked about the trauma history; that's also very important, and other factors. I just wanted to put things into a little bit of a framework here as we're thinking about this topic. And I'd like to thank a bunch of people in my lab who have made this happen, so thank you.

DR. HERNANDEZ-DIAZ: Thank you, Dr. Comer.

We will continue now with an invited guest speaker presentation with Dr. Bobbi Jo Yarborough.

Guest Speaker Presentation - Bobbi Jo Yarborough

DR. YARBOROUGH: Thank you to the FDA and the committee and guests for allowing me to share my work with you. I'm going to be talking about a paper that we published a couple of years ago describing patient-reported pathways to opioid-use disorder.

We know already a lot about who is at risk for developing an opioid-use disorder. We know the clinical, demographic, and prescription

characteristics that are associated with development of opioid use. A lot less is known about how individuals develop problems with opioid use.

In the absence of prospective studies documenting the process by which individuals develop an addiction, patients' recollections of their pathways to an opioid-use disorder serve as a starting point for developing a better understanding of how individuals describe and explain or understand their substance-related problems.

In this study, the qualitative analyses that I'm going to be sharing our a part of the larger mixed methods study of the adoption of buprenorphine across two health systems. In the larger study, we were interested in understanding patients' experiences with and preferences for opioid-use disorder treatment, including agonist treatment.

This was a mixed methods study of patients with opioid-use disorders at Kaiser Permanente

Northwest in Oregon and Southwest Washington and Kaiser Permanente Northern California. The data were derived from health system members' electronic health records from questionnaires and structured interviews. Individuals had to be at least 18 years old and have at least 2 opioid dependence diagnoses in their electronic health record in the previous 12 months to qualify for inclusion in this study.

We did face-to-face interviews, which lasted about an hour. We asked open-ended questions about treatment experiences, knowledge and attitudes about opioid-use disorder treatment and preferences, and then costs and barriers to treatment. Participants were not asked explicitly to describe how they perceive the development of their opioid-use disorder or to provide a detailed history of their opioid use.

The pathway descriptions that I'm going to be sharing arose in the context of discussing opioid treatment histories. And real importantly for this meeting, no dose information was collected

because this was a study of people in treatment, and we weren't concerned in the larger study with what dose they were taking. Transcripts were coded using inductive open-coding techniques. Instances of the descriptive code opioid problems, development, and identity were evaluated using modified grounded theory to identify emergent patterns. Of the 283 participants we interviewed, 121 described at least one pathway, and from that data, we were able to derive 5 distinct pathways.

A little bit about our sample, they were mostly female; 8 percent reported Hispanic ethnicity; 15 percent reported non-white race; and mean age was 39. Three-quarters were currently undergoing substance-use disorder treatment, more than half reported daily or constant pain, and almost a quarter reported that pain interfered with their work in the last month.

When we asked them about their problems with opioids in the last year, three-quarters reported problems with prescription opioids, 17 percent with heroin, 8 percent with prescription opioids and

heroin, and 3 percent who reported no past year opioid problems.

Our first pathway, inadequately controlled chronic physical pain leads to misuse. Here's a quote from one individual. "After being on oxycodone/acetaminophen for a year and a half, I felt like it wasn't working anymore. My doctor said, 'No, no, don't lose hope. Okay, take 8.' I was still taking that amount, but I couldn't make the pain go away. So I began to take more thinking I could cure myself. Instead, I wound up here in treatment. I would never wish that on anybody."

This shows a pattern of misuse can develop even under a physician's care if individuals increase their dose as a part of self-treatment of their pain.

A second pathway, some individuals are vulnerable to opioid addiction even after brief opioid exposures. "I was 18. I got my wisdom teeth pulled, and then I got a script for hydrocodone/acetaminophen, and just pretty much fell in love with it. My first reaction was to

take more than 2. I'd take 6; you know, that's just my mentality at the time. So I did, and it felt great for a minute, and from that point something clicked inside of me, and that's how I wanted to feel all the time."

Another pathway, prior substance-use problems and introduction of prescribed opioids. This person said, "I've gotten bad headaches. I had a doctor who would give me a shot of merperidine hydrochloride, then she switched me to a different doctor. That doctor said, 'I don't do injections in the office, so here's a prescription for 20; take them home, and here's a prescription for 100 hydrocodone/acetaminophen.'

"I wasn't very honest about I'm an addict. I think I told her I did have a history, but I don't know if she just didn't understand addiction and I just didn't bother hammering home, 'No, you really shouldn't give me those.' I went ahead and took them, and, yeah, I was able to refill those way too often."

A fourth pathway, relief from emotional

distress reinforces misuse or abuse. This person said, "I was taking care of my dad during the day, and my mom, and working the night shift as a nurse. And I hurt my back, and it seemed like at that point, my body just went through this chronic pain thing. I found that the pain medication made me feel better; not just relieve the pain but made me feel better, like it treated the depression or whatever. So then I would take them, and of course you have to take more and more, you know."

Then finally, recreational initiation or non-medically supervised use of opioids. "My arm hurt really, really bad. I didn't have any medical benefits at the time. A friend of mine said, 'Try one of these. It might help you.' It was an extended-release oxycodone. It was a 40 milligram, and about a half an hour later, that's really amazing. Then the next day, 'Do you want another one?' Sure. Then the next day, there was 2 of them, then the next day there were 2 of them, and sometimes 3. She had a prescription of them. She wasn't trying to get me addicted. She was just

trying to help me."

Through these interviews, we identified multiple pathways to addiction. None of these are novel. Nobody's surprised by these themes, but they do highlight that addiction pathways are complex and that there are a variety of ways to arrive at an opioid-use disorder.

Ignoring for a moment those who began using opioids recreationally, which was the largest group in this sample, there are a lot of assumptions that are made about how people get from being a pain patient to having an opioid-use disorder. We see here that often people are looking to avoid pain, whether that's physical pain or emotional, and opioids provide a reinforcing relief, which we just heard about.

There tends to be a belief that if we take care of high-dose problems, if you just use low-dose products, or you limit the duration of prescription opioid treatment, you can avoid addiction. We saw in our data that even with presumably low doses and brief exposures, for

example after a dental procedure, it still led some people to seek additional opioids and subsequently develop problems. Then we already know about being cautious when prescribing to individuals with known substance-use histories, and we know clinicians don't always have or seek that information.

I think I was invited here to share the patient perspective and also to remind everyone of the broader context in which opioid-use disorders develops. I think the message here is that there are varied pathways to opioid addiction to keep in mind, even while discussing a very specific pathway through high-dose products. Thank you for your time.

DR. HERNANDEZ-DIAZ: Thank you.

We will now continue with an invited guest speaker presentation with Dr. Hilary Surratt.

Guest Speaker Presentation - Hilary Surratt

DR. SURRATT: Hi. Thank you, everyone. I'm really honored to be here today and share some of the work with you that we've been doing around opioid misuse, nonmedical use, and diversion. I

just want to mention this is largely in a community context, so I'm going to talk from kind of a different perspective than we've heard for a lot of the day. Just to point out here, a lot of the work that I'll talk about was funded by NIH, so I want to acknowledge the funding agencies here, and beyond that, I have no conflicts to report.

I think that I was overly ambitious in the number of slides that I put together for this presentation, so I'm going to move through this background really, really quickly. I think it's been talked about a lot today, so I don't really need to belabor it, and I'll get on to some of the data that I want to talk about. But suffice it to say that the point that I wanted to make here is that in the community context, I think there's comparatively little data that are going to speak to the role of dosage strength in opioid misuse.

So there's not a lot to draw from, so what I hope to do today is piece together some snapshots from various studies and help us understand how dosage strength, among other factors, might

contribute to nonmedical use.

I was really asked to speak from an ethnographic or qualitative perspective, so a lot of the data that I'm going to share with you today, like the last speaker, is qualitative in nature, drawn from a number of different mixed methods studies. I think qualitative data will help us understand and identify a broad array of contributing factors when we look at opioid misuse, and really allow us a deeper dive to understand decision-making that users go through when they're considering these.

The first study that I'm going to talk about is way back in 2006, and then I'll span a number of studies that bring us up to the present day. This was actually a study that we did in Wilmington, Delaware in 2006, and at that time, I was affiliated with the University of Delaware and also the RADARS system. I was part of the team of investigators that was looking at drug diversion and the drug diversion program. I won't go through the background of rapid assessment. Suffice it to

say, it's a very well-used epidemiologic technique.

At that time, we had noticed a spike in the diversion of pharmaceutical fentanyl, and we decided to further investigate the signal or the spike by going into the community and conducting a rapid assessment, which largely involved qualitative research methods to really understand what was happening in the community that would have caused that.

We did focus groups with treatment clients, law enforcement, treatment directors, and a variety of perspectives that we gathered. I'm not going to present all the data today. They were published in the Journal of Pain Medicine in 2009, so it is available for folks who would like to know more. But what I want to focus on is the qualitative findings from the focus groups with misusers and what we really learned from that in this early study.

I think it was important to help us identify several factors that people considered as they were engaging in misuse. What we really learned was

that there were several factors very important for folks. Those were things such as safety. They actually think a lot about safety of medication they're taking; consistency of what they're taking; ease of access; and acceptability. All of those are considerations that people think about, so I think it's important for us to bear that in mind as we look at this.

People talked a lot about ease of access, and we've heard a lot about that today. Especially at this time without a lot of awareness, people were readily able to acquire these medications, from family members, medicine cabinets, and what have you. These were largely low-effort acquisitions and low risk. There wasn't a lot of risk involved as opposed to doing street buys. So those were really factors that people thought a lot about.

Also, from the focus groups, we learned, in this particular case, that there were some nuanced findings around price. This is an early study, but already we're seeing cost pressures on prescription

drug misusers, where they're talking about shifting to illicit drugs away from prescription opioids because of being priced out of the market so to speak. So there are certain drivers that we're seeing and also barriers to this nonmedical opioid use.

Then some specific findings really around the fentanyl issue, which was the impetus for us doing the rapid assessment in the first place. Among this group of users, we found that the fentanyl patches were actually highly sought after, so you might say that demand for them was fairly high. But it's interesting to look at the nuances around it and understand demand versus actual use.

When we started to drill into those findings and really look at it, price was obviously a factor, as was access, although they were sought after and popular for a number of reasons. One was potency but also versatility around how it could be misused. People reported different ways of using it, and that was important to this particular community of users. But when you actually looked

at use, you saw that the IR oxycodone products were much more likely to be misused, regardless of demand. There was sort of a hierarchy that emerged in terms of demand and also what was actually misused.

I'm jumping ahead, but it's in sequence. We had a really large four-year NIH funded study and really focused on prescription drug diversion. This was carried out in several counties in south Florida, between 2007 and 2011. This was, at the time, one of the largest studies NIH had ever funded around prescription drug diversion.

In this study, we recruited more than 1600 individuals from the community who were reportedly misusing medication. This was not focused only on opioids; this was any sort of psychoactive prescription medication that they reported misusing. The real focus of this study was to understand how people were acquiring medications; what were their sources of diversion. But we also asked a number of pertinent questions related to specific opioids they were using and motivations

for misuse that I think are pertinent to the discussion today.

We had 6 subsamples in that study. I'm not going to belabor the methods here. Suffice it to say that we selected these subsamples based on pilot data or previous literature that suggested high levels of involvement in prescription drug misuse.

I present some data here from 782 people. That's roughly 48-50 percent of the overall sample, and these are the folks who reported nonmedical prescription opioid use as their primary drug. This is a large table. I don't want to get into the weeds here. I just wanted to point out a couple of things from this table that I think resonate with what other speakers have mentioned.

That is that in this community sample, we have nearly two-thirds who self-report severe pain in the past 90 days, so clearly that's a factor here. Also, you'll notice heavy polydrug use. I would say that that's a theme in all of the studies that I work on. You rarely find a person who's

only exclusively using one substance; it's largely polydrug use. Again, we don't, unfortunately, have data on dosage strengths reported by these folks, but you'll see again that the IR oxycodone is by far the most often reported, and the high potency, your hydromorphones, fentanyls, much less likely to be reported.

Again, I mentioned that sources were one of the major reasons why we were undertaking this grant effort. Again, they're not mutually exclusive, so people reported sources for their primary opioids. Dealers and sharing and trading are by far the most common sources, and you really see medical practice playing a much smaller role in this particular sample as a source of acquisition.

Again, another big table, but my point in showing this is across the top you have the source of acquisition. Then in the left-hand column at the bottom, we looked at their primary opioid that they were misusing, and this is a logistic regression looking at source. Interestingly and perhaps not all that surprising, you see that folks

who have reported hydrocodone are much less likely to obtain that from a dealer. It's only when you get into the ER oxycodone that you find a difference, people less likely to obtain that from a legitimate medical provider.

So you do see that the opioid that they're using and the source have some statistical relationship, which is also important to keep in mind as we're thinking about the range of factors that is impacting these samples.

I'm going to jump quickly into the third bullet here just in the interest of time, because part of this study, it was a mixed methods study. We interviewed prescription drug dealers with in-depth interviews as part of this study. We interviewed 50 ethnically diverse prescription drug dealers, and we were really interested in understanding their sources, how they come to their supplies of prescription medications.

It was through that work that we really identified the role of pain clinics in south Florida, in this era, which was pre-2011, as a

major source of the supplies that dealers were then selling on the streets in south Florida. Actually, now that I'm in Kentucky, I will say that I've been on both ends of the transit of pills from south Florida to Appalachia, which I'll talk about in just a minute here.

Really, these pain clinics, as we all recall, they were very numerous, and there were large prescriptions being written day after day after day. The dealers really leveraged those pain clinics as their primary source for prescription opioids that they were then reselling.

This is a very wordy slide, but it was some of the most clear data that we had around the popularity of the high strength opioids. In this case, it was the 30-milligram oxycodone immediate release, and also we had some discussion of the 80-milligram OxyContin pills here.

Not at the user level did we see that, but when we were at the dealer level, who again are operating an organization for profit making activity and working with pain clinics, you see

that for profit making, they were certainly the most interested in those high dosage strength pills. They also mentioned other factors as well, being that they really preferred the single-ingredient formulations because of popularity and demand on the street, so to speak.

Also, another subsample that we did within that larger umbrella of the diversion study, I showed earlier that one of our samples was an elderly sample, which was 60 and over; and as I get closer to that, it seems less elderly. We took mixed methods approach there as well and did some qualitative interviews with our sample.

I will just mention here that the mean age of the sample was 63 years. They were primarily male. Again, you see the theme around physical pain. This sample in particular, there was a high prevalence who reported that they were misusing their medication for pain. You also get a different snapshot of the specific opioids that they mentioned. Although there's a lot of IR or ER oxycodone, tramadol and hydrocodone, much more

prevalent in this population.

Here I just show another table on our elderly sample, again to show you that the source matters. People who were going to their regular doctor were largely more likely to obtain tramadol. There are these differences that I think are important to bear in mind, because when we got to the qualitative interviews with our elderly sample, like the previous speaker, I think we identified some of the same kinds of themes around misuse of their legitimate prescription because their pain was undertreated. So I have several quotes here, that I won't mention, of individuals who mentioned not being able to obtain adequate pain relief, making that transition to misusing their own prescriptions.

Another theme already in this sort of era was physician reluctance to actually prescribe higher doses or higher potency medications, and this was adversely impacting this sample of patients.

Actually, I don't display it here, but there

were several people from this sample who also then talked about seeking oxycodone in particular on the illicit market because the tramadol or whatever they were actually being prescribed was clearly insufficient to meet their need, and I think that's a theme that's been heard more than once today.

Quickly moving along, a subsequent study to the diversion study that I just talked about, also in south Florida, was among young club drug users. This had a different focus, obviously, but we had documented over time in the south Florida context that within the club scene, misuse of prescription drugs, including opioids, was highly prevalent.

This actually was an RCT designed to reduce substance use with a low-intensity intervention among young club drug users, but within that context, we continued to be able to monitor prescription drug misuse, and opioid misuse, or nonmedical use in particular. Again, these were fairly young folks, ranging in age from 18 to 39. They reported use of club drugs and misuse or abuse of a prescription medication in recent history.

This analysis that I am presenting was actually published in Drug and Alcohol Dependence in 2017, and it looked exclusively at the portion of the sample that reported nonmedical prescription opioid use, so it excluded folks without that endorsement.

I really apologize for the font size on this table. What we were actually looking at was the role of nonmedical prescription opioid use in transition to heroin in a sample that was actually largely recreationally using opioids, and we just wanted to look prospectively across our follow-ups to see what that would look like and what factors might be key in that transition.

One thing to note that I've said to everyone who will listen is there's heavy polydrug use in this sample. It ranges in substance and it's largely opportunistic. They do a lot of their purchasing -- as you'll see in the bottom when you look at sources -- like direct buys within the clubs. There are pills packaged together, and a largely opportunistic purchasing.

I think it's interesting to note here also, when we looked at days of nonmedical prescription opioid use, and also in particular the route of administration, we did find that people who were tampering with their opioids, including just oral tampering -- so crushing but then swallowing -- actually were more likely positioned [indiscernible - mic fade] to heroin.

So again, that's not dosage strength in particular. but we were noting a number of other factors that seem to relate to problematic use, and transitions, and shifts that we think are important to bear in mind, and we look at this in a complete picture.

I'm going to move through that and just moved to my current situation. In 2016, I went to the University of Kentucky from south Florida, which was a difficult transition; although I'm from Kentucky originally, so that made it a little bit easier. I have a study that's funded by NIH to look at uptake of syringe exchange or syringe service programs in Appalachian Kentucky.

Many folks sitting in this room I know are aware that Eastern Kentucky has had a longstanding opioid problem, opioid endemic. We've experienced a lot of adverse health consequences as a result, including rising hepatitis C, NAs, and a number of consequence that have really impacted those communities. So I'm just drawing some data from that study quickly to give you a picture of what it's looking like now that I think is pertinent to our discussion today as well.

Here's a map of Kentucky. This is actually overdose death rates. We've had a very serious problem with overdoses, and we were actually really fortunate to be awarded recently a healing community study that will target reductions in overdose fatalities. It's a very ambitious project Sharon Walsh is leading, and the goal is to reduce overdoses by 40 percent in 3 years, so we have a lot of work to do.

I am working on this study that I'm reporting on now in three of these Eastern Kentucky counties where you see significant impacts of

overdose deaths. I'm not going to go into the history of syringe programs because I feel like a lot of people in this room are well educated on the topic and have a lot of good experience with those programs, but they're really largely evidence-based structural HIV, hepatitis C interventions, and I'm glad to see them coming to Kentucky.

Just to mention, these are rural, small counties, but they're heavily impacted by opioids historically. This was surprising to me. This slide, we asked folks who came into these programs -- and this was all collected during calendar year 2018 across the three counties -- what is the primary drug that you have injected in the prior month?

That second bar is methamphetamine. The bars are broken out. The blue, that's the only drug they report injecting in the past month; orange, that's the primary drug; and gray, it was secondary, they injected it, but it wasn't their only or primary drug. When you see the bar for methamphetamine, it blows away all of the other

substances that we were asking people about.

The second most prevalent was actually non-prescribed buprenorphine, so diverted buprenorphine, followed by heroin, which is the first bar. And then fourth, there's the non-prescribed opioid. So it's actually a much lower prevalence in this high-risk sample of injectors. Proportionately, many, many fewer report that as their primary drug of injection.

Just to sum up from that, I think one of the things that I wanted to point out, at least in that context of Eastern Kentucky, which has typically and traditionally been kind of a hotbed, I think that other drugs have largely supplanted prescription opioids recently, and I think that's occurring in the context of a lot of state initiatives and healthcare initiatives to reduce the days, for example, that drugs are prescribed and other measures that are being undertaken. I really see that it's having some impact.

Now, these are snapshots, so it's not a longitudinal study. But if you look at the work of

Jennifer Havens and others that have been doing studies with injector populations in that area for many, many years, the prevalence of prescription opioids used to be a lot higher. So I think there is some impact there, and we're largely seeing a shift.

Qualitative data from folks around this -- and to me, at first it seemed kind of nonsensical because meth is not an opioid, but people are finding ways, in a street context outside of medical channels, to navigate the issues that they're having. We see barriers for folks.

This individual in particular talked about back in the day having traveled to Florida to obtain prescription pills and is now using meth, and finds that he just doesn't think about it. So it's all how you think about the realities that folks are experiencing. I'm not going to belabor this; another person who mentions that they couldn't afford this prescription habit and now she is also using meth.

Finally, an interesting quote that I found

related to the discussion around buprenorphine, and we saw the fairly high prevalence of nonmedical buprenorphine in the community. This person talks about using it as a shield. This is not a lone voice. A lot of people talk about it in this way, that they use it because it prevents them from doing other things; in particular, taking a shot of heroin or these things, and it just normalizes them, and that's how they're sort of navigating or self-treating.

I would also just add -- I know I'm probably going over time, and I apologize -- as part of this study, I interviewed community stakeholders. So I had the chance last Thursday to interview the sheriff and a narcotics detective in one of my participating counties. That detective has been in his role for 16 years. He was a great historian, and he had a really good sense of the different waves and epidemics that have impacted his community.

He told me it's fairly clearly an economic issue. He says that his problems are heroin and

meth. He rarely sees prescription pills; a smattering here and there, but it's not a primary focus of their investigations. He said it's largely economics.

In his view, for a 30-milligram immediate-release oxycodone on the street in his county right now, it's 45 [dollars] to $50 street price. You can get a tenth of a gram of heroin for $30, which he equates to three 30-milligram immediate-release oxycodones. So if you just simply do the math, from his perspective, those are where his problems now are. The supply is fairly limited. They're scarce and very costly.

That was a little bit of an aside, but I think it's important to get that law enforcement perspective because they really are on the street and understanding what the market is like in their area.

Conclusions, clearly, I would say, based on this sort of a review of studies that I've been involved in, nonmedical prescription opioid use, largely opportunistic. It actually is impacted

by -- there are multiple contributing factors that just we've seen in our data: cost; availability; potency; ease of use; safety; amenability to tampering; single-ingredient formulation; diversion source; all of those play into decisions among users around this issue.

Obviously, some segment of our samples are really heavily impacted by undertreated pain, so it's difficult to really disentangle misuse and undertreated pain motivations because they're actually fairly prevalent in all of our samples. How that actually relates to use to get high, the distinctions are not as clear as we might hope.

All of the studies we reviewed, the most common, misuse and diverted, were not those of highest potency. Now, I don't have dosage strength in all of my work, so it's difficult for me to comment on, but clearly there was some demand for these high dosage strengths among dealers. They're in a profit-making business. But at the individual user level, no real compelling evidence around dosage strength, in particular, as the driving

factor.

I'm just going to stop there because I think I've gone over time, so thank you so much.

DR. HERNANDEZ-DIAZ: Thank you very much.

We'll now continue with another invited guest speaker presentation with Dr. Theodore Cicero.

Guest Speaker Presentation - Theodore Cicero

DR. CICERO: Thank you very much for inviting me to come and talk about the trajectories of substance abuse, and this is a big tall task. I think you've heard some of this discussion today, but I'm going to try to cover a bigger study we've been involved in for 25 years now, looking at 30,000 people who have entered a treatment center in one of 149 treatment centers around the country.

Of those 30,000, we asked a number whether they would give up their anonymity and actually talk to us one on one. The initial screening is actually given on a questionnaire, and then if they want to go beyond the questionnaire, they can go ahead and fill out this card, and we'll treat them

anonymously at that juncture.

I think the importance of the questionnaire was in the very beginning, we had calls from people -- this is back in the late 1990s. We had calls from people saying you're asking the wrong questions, and our response was, "Okay. What are the right questions?" And they gave us a lot of information. Most of our research has really being qualitative, not quantitative data because we're dealing with 30,000 people, but quite a few people that actually were willing to talk to us and give us straight information.

The common opioid trajectory -- and this is really an oversimplification -- started with initial exposure, which leads to euphoria, typically. Then there are other benefits, which I want to cover a little bit. Then I'm going to get into tolerance, and there are three choices that people make after tolerance develops, either stronger or they use illicit opioids. They increase the dose or the amount if they can, and now routes of administration, injection, snorting,

this sort of thing, and then they go into a maintenance phase.

Okay. What's the initiation of prescription opioid abuse? We have both patients that started with opiates, then we have also people who just did it recreationally. This person, "I was prescribed Vicodin for pain, associated with a kidney stone when I was 14. It not only took away the pain, but made me feel really good all over. I had smoked pot and drank before but nothing compared to the feeling Vicodin gave me." We hear this over and over again.

This is the most distinct comment we've gotten and probably the most complex one. "It felt like God was petting me." Now, for me, that was difficult to envision. I'm not quite sure what he meant by God was petting him. So I asked questions about it, "What do you mean by that?" And actually what he pictured was God in robes and holy, close to his chest, stroking his hair, making him feel secure. He was able to get away from his problems, and God was taking care of him. It's a very deeply

held feeling, and, really, I think shows some of the power involved in this drug.

There are unanticipated benefits of sustained use. Of our population -- again, we're looking at 30,000 people -- 73 percent, whose first exposure was a prescription opioid, reported that they had treated a psychiatric issue; 67 percent of first exposure being a nonprescription was about the same. So almost three-quarters of our population have treated actually to rid themselves of psychological or other psychiatric issues.

"Have you ever used opioids as a means of escaping from life?" about 85 percent did in fact. And that reference to God before, again, a lot of people are really just seeking to get away from their current circumstances. They can't stand the circumstances they're in. The comments typically, "Finally relief. Not only for the pain of the broken collar bone, but most importantly for my mind. I love the feeling of euphoria. I finally felt comfortable in my own skin. I could talk to anyone. I felt what I was supposed to feel like.

Extremely happy. I knew I had found the secret to my success. Well, I was wrong, it ruined my life."

"Forgot about shame, forget about failures/shortcomings, to get relief from the personal burdens/struggles, distract self from inner peace."

"The escape was from the real pain I had from the back problems, but it also allowed your mind to release and think in comfort, rather than a stressful way. I have never been as successful or motivated or feel as good as when I was on opioids."

We hear this comment over and over again. A lot of these people have relapsed 4 to 5 or 6 times. They really do get relief of that stress, and they feel that they really are much better people when they're on opioids than when they're not on opioids. That's a very distinct feeling from all of our studies, and they really actually think they're better people.

The tipping point that turns from what we just described here to maintenance, after a very

short period of time, people are saying, "If I didn't have it in my system, I was throwing up. I was extremely sick. I didn't have oxycodone/hydrochloride or oxycodone, or the methadone. I was dope sick. I thought I was going to have a heart attack. Your heart races. You're shaking. As long as I had it my system, it was okay."

Clearly, withdrawal sets in, and most of our people will tell us that they're now taking the drugs simply not to get sick. They really don't get high anymore. They have no illusion of getting high anymore. They just don't want to get sick; another quote to that effect that's in your handout material.

The route of administration is very important. We know that people use different routes. They use oral routes or non-oral routes of administration. You can see from this figure here, the oral initiation, about 87.5 percent of the people use the oral route of administration. This is what they started with. Very few people,

8.9 percent, actually start with a non-oral initiation. Usually it's snorting or smoking. Very rarely do people inject at the first exposure. It's really taken by an oral route.

You can see in the oral, the left panel there, the non-oral initiation, a lot of people actually move on to that from oral presentation or oral ingestion; not so much going back and forth with the non-oral route of administration.

By and large, what we always seem to ignore is the fact that most people are abusing these drugs by the oral route of administration. We talk about abuse-deterrent formulations. We talk about all the rest of it. They're really protecting against initiation by smoking or snoring, or IV administration. Most people take the drug orally. And we've got to remember that constantly; that this is the primary mode of action.

How do users cope with tolerance? Use of multiple pills is the easiest answer. What we see here in this RAPID [indiscernible], quite clearly, maximum number of pills swallowed, we have people

taking up to 10 to 20 pills several times a day, really massive doses of drugs; 85 percent cited accessibility or availability as a driving decision to swallow multiple pills instead of using fewer pills of a higher dosage.

Obviously, this is going to play into your discussion to some extent because, actually, a higher dose strength would be very appealing to this group of people. Rather than having to take multiple pills, they could take just a single pill. I'm not advocating that in any way because I think it's a downside for patients.

"Only to obtain a certain milligram without paying higher rates."

"I didn't want my addition to be obvious by asking my doctor for a higher dose." That was a lot.

"I couldn't get a higher dose from the doctor, so I improvised and took more pills to get the desired effect I was after."

Here are the top 10 drugs that are used when adjusting multiple pills, number one is hydrocodone

and IR oxycodone. The only ER drug up there is really oxycodone extended-release tablets. A lot of the drug abuse is blamed in the introduction of oxycodone. It still retains a great deal of popularity, but most people prefer immediate-release drugs. They really don't go for the extended release if they can avoid it.

Why not use oral routes of administration? A logical question. Fear and discomfort of non-oral routes, 45 percent. "I did not want to smoke, snort or inject them because I was afraid of the risk, that I would then want to use and try heroin."

"I kept wanting to do it as prescribed, even though I may have take it more. I didn't feel like an addict if I did it this way."

I think the last reason there is symbolic of a lot of questions. "It is more socially acceptable to pop a pill in my mouth, than it is to shoot up in my arm." Particularly, if you're working or you're around your family, people do not want to be associated with an injecting portion.

They would rather just be able to pop a pill. The stronger the strength of the pill, obviously, the better off they'd like it.

Oral methods that are sufficient to attain the feeling of high, you'll see that mentioned quite often; lack of desire, want to use non-oral methods. People are just never interested in taking opioids in that manner. A lot of people are afraid of needles.

Option 2, non-oral routes of administration. Why not move on to the non-oral routes of administration. In fact, the motivations for people that did want to move on, they wanted to get a better high, actually. Initially, they really were looking at tolerance and they're trying to overcome the limitation of oral administration, but a lot of people just wanted to try it to see what high they could actually get from it. They wanted to obtain a quicker high as well; curiosity. You can see the reasons listed there.

I'm trying to get across that the feeling when you leave these data that a lot of these

decisions are based on the individual characteristics of a drug. That really depends on what's available and the characteristics of a drug, which even when you predict drugs should be the same, like hydrocodone and oxycodone should be roughly the same, they're really not when you an analysis of it.

Deciding between oral and non-oral routes of prescription opioids, the specificity of a drug. One drug, this point again, "If it was hydrocodone, I would chew them. If it was something like Percocet, I would snort it. If it was instant release like Roxicodone, I would sniff or inject, usually inject. Dialaudid would be injected. Morphine and Opana would be orally." "The harder it was to break down, the harder it was to shoot up."

I think this last comment here on this page -- and again, this is all in your briefing materials -- "It depended on the bioavailability of the drug. Opana is useless orally, but gets you very high with other methods. Oxycodone is one

that I feel much better high if I take it orally."

So there really are differences between the drugs, which are quite subtle. We all know about the Opana crisis that occurred. There is no practical pharmacologic reason to explain that, exactly. They should have been equivalent in likability, but they're not for some reason. The folklore or whatever it might be, that IV Opana is wonderful compared to anything else, it persists, and it's not quite clear why.

Non-drug related factors, again, a better feeling. "Once I got deeper into addiction and my inhibitions lessened toward injecting, I would choose to inject due to the better quality and more immediate high."

"Orally is better to hide when you're around family or coworkers."

"The amount I was going to take and how much powder they would break down to. Sometimes it would be just too much powder to snort." So a lot of practical considerations, too. They chose the routes of administration based upon a lot of

practical concerns, availability and other sorts of issues.

Drivers of prescription opioid selection, I think this is really an interesting slide. If you look at immediate-release opioids, 66 percent of the people would prefer immediate-release opioids than anything else. Extended-release opioids, surprisingly only about 4 percent of the population indicated they would prefer those initially. They might have graduated from them later, but at least, initially, the extended release were not very attractive to them.

There were a percentage of people, about 30 percent, that had no particular preference. They would do them orally or non-orally. Again, 98 percent, lifetime use; immediate release, about 91 percent of ER. So they are used. ER are used, but they're less much less frequent than immediate release.

Here, look at the primary drug use patterns in opioid-dependent individuals. What I really focused on here is hydrocodone and oxycodone.

These are fairly sizable numbers of people we actually interviewed, looking at both hydrocodone and oxycodone. Again, the prediction would be these drugs are roughly equivalent in potency. They should be equally attracted to an addict one way or the other.

You can see there are lots of differences here. I just want to focus on one of them. The reasons for selecting hydrocodone or oxycodone, the quality of the high is a striking difference between hydrocodone and oxycodone. Obviously, oxycodone was viewed as giving a much better high than hydrocodone; again, no rational reason. One would not predict from clinical or preclinical studies that there should be a difference here, but there clearly is in humans. Easier to get is certainly a factor. Hydrocodone is in plentiful supply.

Conclusions, wrapping up quickly here, every drug is unique. I think you have to really understand that. As you move in the rest of your discussion, every drug is going to be unique, and

what we think we can predict now won't necessarily be the case. When it's actually released and available to millions of people, then we're going to find out something quite different.

Predictions of abuse potential are guesses at best. I hate to say that for people doing a lot of this research, and I'm not demeaning it at all because it's very quite useful to look at predictions of abuse potential. But it really is a guess at this juncture. I can't explain a lot of these differences we've seen, but there are just drug differences. I'm not clear why there are drug differences, but there are. The role of high dosage opioids, they're still not well understood in both pain patients and opioid-use populations.

High dose opioids, obviously, the advantages are plentiful. You've heard plenty of reason this morning for the use of these medications, particularly for a high-dose strength drug that would be very useful for people who had to take multiple pills every day. Certainly for the elderly and cognitively impaired, not having to

count pills, as you saw my illustration 20 pills at a time, if they could take a much higher dose strength, that would be an advantage for them.

The higher dose, the advantage obviously is being able to take a single pill in place of very many. The disadvantages, of course, the higher dose strength solves the tolerance problem for abusers. I think we have to realize that if you have a dose that's 80 milligrams and they're used to taking Vicodin at 5, as they develop tolerance, they're more likely not to take 20 Vicodin, but they are more likely to take one pill at a much greater strength.

It's a complicated decision. Again, it depends upon the drug that you're looking at that, which will determine routes of administration, whether that gets abused or not. With that, I'll wrap up.

DR. HERNANDEZ-DIAZ: Thank you very much.

We will now continue with another invited guest speaker presentation with Dr. Bruce Goldberger.

Guest Speaker Presentation - Bruce Goldberger

DR. GOLDBERGER: Thank you. It's a pleasure to be here, and thank you for the opportunity to speak today. I am chief of the Division of Forensic Medicine in the Department of Pathology at the University of Florida College of Medicine.

This principle of dose and effect is not new, as you probably know. If you go back 500 years or so, Paracelsus made the association between dose and poison. That principle was affirmed about 150 years ago by Taylor, when he said a poison in a small dose is a medicine, and a medicine in a large dose is a poison. So this is not new at all, but our problems today are different than back in the 1800s for sure.

This is a headline that you probably had seen many months ago from the New York Times. Writer Sanger-Katz has been studying and publishing a fair amount of data, primarily from the CDC but from other sources, too, on the opioid epidemic or crisis. She had reported that estimates for 2017 would reach a record of 72,000 overdoses.

I think the figure underestimates the problem because of the lack of investigations that are done in the field, both by medical examiners and coroners, and I'll speak to that later, but certainly, probably, a figure greater than 72,000. I just can't quantify it for you.

This is also from her article, and you've seen this before. I'm certain where we've seen this dramatic rise in synthetic opioid deaths. That's principally fentanyl, illicitly manufactured fentanyl, beginning in about 2014 into 2015.

This is a CDC slide from some of my colleagues there, Margie Warner, in particular; so thank you, Margie. This slide demonstrates the three waves of rise in opioid overdose deaths, beginning back in 1999 with the first wave of rise in prescription opioid overdose deaths, principally oxycodone and hydrocodone back then. In the second wave, which began about 2010, was the increase in the heroin overdose deaths. This current wave that we're in right now, which began in about 2013 or '14, associated with synthetic opioids, principally

illicitly manufactured fentanyl and fentanyl analogs.

I believe there's actually a fourth wave that we're entering right now, not necessarily opioid, but opioid related, which would be opioid plus stimulant, and that would be methamphetamine and/or cocaine, which I'll touch on in a minute.

The medicolegal death investigation process unfortunately is not standardized across the U.S. We have medical examiners, and we have coroners, and we have multiple jurisdictions. We have centralized offices and decentralized offices. Our system in the U.S. is not optimal for the proper assessment of these types of deaths, but we're getting better, and I'll talk about that later today.

When a medicolegal death investigation is started, and if it's a suspected drug overdose case -- or hopefully not only suspected drug overdose cases, but in Florida, for example, nearly every case that is autopsied by a medical examiner will be drug tested as well. That's not true in

all states. There will be testing for volatiles like alcohol, tests for over-the-counter drugs, prescription drugs, and illicit drugs.

When you look at lab to lab to lab, there are huge variations. What you see tested here in Maryland, for example, it is a statewide system run out of Baltimore, and then you look at Florida, where we have over 20 offices, there's a huge variation in what is done on a per case basis.

I can say for certainty, or at least I hope now in 2019, that all medical examiner and corner cases are tested for the following drugs on this slide. The one drug that I think I could bracket would be buprenorphine. Not all jurisdictions test for buprenorphine, so we really don't have good death numbers or mortality assessments of buprenorphine, but I'd say all the other drugs are commonly tested for in all pending toxicology cases.

Now, we do have new drugs. Well, let's go back a sec. We have the illicit drugs, which include marijuana, cocaine, heroin,

methamphetamine, and PCP. I read in the paper today that someone died from marijuana in the state of Louisiana, allegedly. I don't think that could even possibly be possible. But that's why it was in the newspaper because I think that was the index case in the U.S., maybe in the world, the first and only person who's died from cannabis.

Now, you can die from the use of cannabis if you're impaired, and you operate a motor vehicle and drive off the road, for example, but generally cannabis is not going to be a cause of death. But cocaine, heroin, methamphetamine, or PCP are our standard drugs, and they all have been around for decades.

We do have these new drugs. We refer to them as new or novel psychoactive substances or NPS. The class that's most commonly known of that would be familiar to you would be the synthetic cannabinoids.

There was a rash of synthetic cannabinoids across the U.S. in corrections, with prisoners getting access to synthetic cannabinoids in

Florida. Although, I don't have the exact counts, we've documented over a hundred of those prisoners using synthetic cannabinoids and dropping dead.

The new fentanyls could be considered an NPS. The terminology of NPS to me lacks applicability today. I don't like the term. I would rather classify it differently, but that's what's been accepted all the way up to the UN level, so that's what we're stuck with. But essentially, those are the new psychoactive drugs.

This class of synthetic opioids that has been driving this epidemic, this crisis, it's not the high-dose opioids I can say for sure that's driving this crisis or even the low-dose opioids that's driving the crisis. It's these drugs.

On the left, we have fentanyl analogs set aside illicitly manufactured fentanyl, of course, because we have tens of thousands of those deaths. But these are the analogs that you hear about in the news. Probably the one that's most famous would be carfentanil, and the index incident for carfentanil deaths is in Florida in my

jurisdiction, which was in the Manatee County Sarasota area, where in June of 2016, I believe, we began to see 3. 4, 5 people dead a day, and then there was a coincidental outbreak in Ohio a few days later. Presumably, probably the same source of drug from the same source somewhere; don't know where.

In the end, we've seen thousands of carfentanil deaths in the U.S. s now. With carfentanil, it's a small dose, but it's a highly potent opioid, hundreds of times more potent, allegedly, than morphine. I don't know how you would measure that. Some of these measurements were done decades ago by Janssen Pharmaceuticals, and I'm not really sure how reliable they are today and what we know about the science of opioids and analgesia.

But we know that many of these analogs on this slide of fentanyl are highly potent and very lethal. Over on the right-hand side, we have some other odd compounds like U-47700. These are opioids. They don't at all like a phenanthrene

opioid. They don't look like fentanyl or methadone. They have their own unique structure, but they are opioids because they do interact with the opioid receptors.

Moving on to what we see typically in an overdose death, and it's been mentioned several times today by some of our speakers, is that these individuals -- and now I'm speaking to decedents, are using many substances, so these are polysubstance use cases. I would say 95 percent of the cases that I investigate with state medical examiners in Florida would be polysubstance use cases, where there's more than one drug found.

Most often today, it would be a fentanyl analog or heroin, also with methamphetamine and/or cocaine, and maybe a benzodiazepine and alcohol as well. Fatal intoxication is common amongst these prescription and illicit drug users, and today it is clearly polysubstance use. I'll show you some data soon.

I know and I can demonstrate that the number of drugs that are ingested is directly related to

the incidence of the fatal overdose. I'd say the literature might lack that, but when I look at case after case after case -- and in my career, I've looked at 50[000] or 60,000 drug overdose cases -- when you begin to stack a benzodiazepine with a synthetic opioid, with a stimulant, for example, it becomes very obvious to me that that led to the death of the individual, and then you could read the history as well.

Many of these overdoses are accidental. Most of them are actually accidental drug overdoses, and some will be intentional overdoses, suicidal deaths. Most of the suicidal overdoses will be prescription drug overdoses.

Some of the common opioid drug-drug combinations would be an opioid like fentanyl with alcohol, or hydrocodone, or oxycodone with alcohol. There's plenty of data out there in the literature that would support the increased lethality when you mix an opioid with alcohol, and the same holds true when you mix an opioid with a benzodiazepine.

I think there's still some conflicting data

with regards to buprenorphine and the benzodiazepine. When you look at the European literature, there's a clear link between increased lethality or likelihood for overdose when you mix bup with benzo, but I'm not sure that really pans out entirely, and that would need to be studied further. Nowadays, we have fentanyl or fentanyl analog with cocaine and/or methamphetamine.

The question is always what came first? Is it the fentanyl followed by the stimulant or is it the stimulant followed by the fentanyl? What I hear from the street these days is that the users of the opioid oftentimes try to ameliorate the withdrawal with the use of a stimulant. I don't know how true that is, but that's what I hear. We need more research, please, from the streets.

Toxicologically, these cases are relatively straightforward. In the case of an overdose, it's typically the predominant drug effect that results in death. In a case of a depressant and a stimulant co-ingested, they don't cross each other out. I think many lay people think that you can

negate the effect of a depressant with a stimulant; think about alcohol and caffeine, for example. Those are wivestales, and they don't pan out.

These cases are complex pharmacologically because you have the opioid, perhaps a very potent opioid, reacting in one region in the brain, and then the stimulant in another region in the brain. So you can begin to stack the effect, and you can see where we end, where we have many deaths.

The combined drug effect with these is absolutely at least additive and could be synergistic as well. There's been much talk about this today, a frequency of drug administration. Many of our decedents, I'd say a lot of our decedents, are tolerant because they've been using drug for weeks, months, years, decades even.

We do need to consider the use of an antagonist. I don't think that's been mentioned at all today, the use of Narcan. In Florida now, we have in place -- I guess it's probably pretty nationwide now, where you can get Narcan in your pharmacy over the counter. It's not cheap. It's I

think $75 in Gainesville at CVS and Walgreens. And I know a lot of our physicians are now recommending that people have Narcan at home because you just never know when someone might overdose.

These data are from the Florida Drug Related Outcome Surveillance and Tracking System or FROST. This is a system that's funded by BJA, a grant to the University of Florida. We collaborate with colleagues in Kentucky.

This is the state of Florida, a dashboard for drug overdoses. What I wanted to point out for you here is the polysubstance abuse issue. On the left-hand side, go halfway down, and look at oxycodone. There were 610 deaths in 2017. In 95 percent of those cases, there was another drug found in the decedent. The most common drug, to no surprise, would be alprazolam. These data can be downloaded from FROST by anyone. We have lots of data that pertain to drug overdoses in Florida on FROST.

I don't think I really need to mention this, but this is the typical triad of an opioid

overdose, which includes the CNS depression, respiratory depression, and miosis. That all builds up to the building of the typical toxidrome for the determination and certification of the cause and manner of death by the medical examiner and/or the coroner.

It is their job, in a legal context, to establish the cause and manner of death. That must be done in every single death here in the U.S. When that medical examiner or coroner does that, they will, or I hope they will, look at the toxidrome, which basically would be establishing the constellation, signs and symptoms, at the death that could be associated with the ingestion of a drug or drug class.

The typical pathology is straightforward; I'm not going to go through this too much. But many of these cases are complex pathologically because there are lots of underlying comorbidities, which might include heart disease. So it's not unusual, even to see young people who have been using lots of drugs, opioids for example, and

injecting opioids, to see cardiomyopathy or coronary artery disease. Those would be typically listed on the death certificate.

In the final determination of the death by the medical examiner or coroner, I would hope that they -- and I think they do. They do a pretty good job out there. They do take under consideration the potency of the drug and the consideration of the drug interactions. There's been a lot of emphasis by the CDC on the medical examiner and corner community to add greater specificity on death certificates because in previous years, they might just say acute drug intoxication, and then they close it out.

That does very little for people who do epidemiology and surveillance of drug overdose deaths, so now, most medical examiners and coroners will say heroin and cocaine intoxication. They'll begin to specify on the death certificate on line 1, if you're familiar with the death certificate, the exact cause of death and those drugs that are responsible for the cause.

They take under consideration the significance of the autopsy findings and the toxicological findings. They also would consider any interaction of natural disease and drugs, and also consider the medicolegal death investigation findings. Was there a syringe found in the arm, or was there paraphernalia found at the scene, or was the person found on the toilet at the local Walmart with a syringe on the floor? Things like that; those findings are considered by the medical examiner.

This is an area that I've been speaking a fair amount about. In the state of Florida, I worked with the state to get our medical examiners access to the state PDMP. Now we're trying to get them to actually use the PDMP, which is a problem. Just today, I received two messages about how do we get our medical examiners to use and access the PDMP.

I think it's really important for our medical examiners and our coroners around the nation to access the PDMP, so we can get a better

feeling for that transition from licit opioid to illicit opioid. How many people do we know for a fact are using licit opioids in a controlled setting and eventually lead to, or it leads somehow to the use of an illicit drug like fentanyl or heroin, and then subsequently death?

All of you I'm sure are aware of the power of the PDMP, and I really encourage our docs in Florida to use our PDMP. It's not mandatory for a medical examiner to use a PDMP like it is mandatory for a physician to access the PDMP before they prescribe a controlled substance. We haven't gotten there yet. I'm not sure we ever would.

I'll show you a few data slides as I wrap up. In 2012-2013, and leading to '14, the blue line shows fentanyl-related deaths. This was when it illicitly manufactured fentanyl hit the streets of the U.S., and we really didn't have a handle on what it was or where it was coming from. To say the least, we weren't -- meaning the medical examiner community -- communicating well enough with the crime labs and with law enforcement like

we do now because we have groups that we communicate regularly with.

Our state PDMP was really concerned about the medical examiner community issuing a report that now we have many deaths associated with fentanyl, where they're actually going back and looking at fentanyl prescriptions, and that's what we did here. The orange line looks at fentanyl prescriptions beginning in 2011, which was the start of our PDMP, all the way through to '15 or '16, and there not a relationship, thankfully.

We knew that antidotally. I knew that based on reviewing the case reports from the medical examiners, but here we proved it. It wasn't your prescriptions for fentanyl that was leading to this rapid exponential growth of fentanyl deaths on the street, so we were thankful for that.

As many as probably everybody in this room knows that the state of Florida was hit very hard by this increase in the number of pain management clinics. I believe somewhere between 80 and 90 percent of all the oxy prescriptions back around

2010 were being prescribed in the state of Florida. I can't remember the exact number.

You can take a look at the white line, and beginning in about 2006 and '07, the number of oxycodone deaths increased pretty remarkably. Then beginning in 2010, leading into '11 and '12, there were lots of interventions. Many of these interventions were done at local levels where pain management clinics were shut down. They were done at state levels where our statutes were rewritten, so physicians couldn't prescribe and dispense controlled substances. I think they could only give a 3-day supply. Then we had the implementation of our PDMP midway through 2011.

Take a look at the oxycodone deaths. They dropped precipitously as soon as all of these actions were put into place. That's what you see here. We have a steady level of oxycodone deaths in the state of Florida, but nowhere near the number that we had back in 2010 and '11. So those actions plus the PDMP saves lives.

A few slides from the literature because the

task for me today was to tell you what we know and what we don't know. I think we actually don't know enough, but we do know there is some literature. If we look at an article from the British Medical Journal, BMJ, you can on the X-axis is the increase in daily opioid doses. This is milligrams per day. We're always concerned about benzodiazepine use. With benzodiazepines and the opioids, there is an increase in death, in the death rate. I think you're familiar with this data.

I know you can't read the data on this slide, but my point here is there are lots of epidemiologic data out there, tables like this that show you type of prescribed opioid, and the death rates, and patients with active prescriptions, and so on. There's a lot of data out there, but unfortunately the data that's really liking is this transition from prescription opioid to illicit opioid, which is my main concern. We just lack that data.

Here's a slide from the CDC MMWR looking at drug overdose deaths rate and as it associates

itself with the rate of kilograms of dispensing of opioids. Again, you can almost put these on top of each other. The more drug that's dispensed or sold, more deaths.

This is from Archives Internal Medicine, where an association was made, as well, with an increase in opioid-related mortality with daily doses of 200 milligrams or more. This is a slide that shows the incidents for deaths, overdose deaths as the average daily milligrams of morphine equivalents increases. This is a similar slide just showing the interaction between an opioid-only and an opioid-plus benzodiazepine. I am concerned about opioids and benzodiazepines, as I think probably all of you are.

That's a Florida gator. To finish up, my job here today was to talk about what we know and what we don't know as it pertains to overdose deaths. I think we know a lot about why people die. That is the mechanism, and that's no secret. But I think we don't know enough about that transition that I've referred to. I sure hope that

there's funding out there in the future from the funding agencies, and I'm not speaking to the FDA specifically, to look at that transitioning of these people, or the poor decedents, or dead people, and how they got to where they got to.

There's lots of work in improving the medicolegal death investigation process. There are new standards being written for medical examiners and coroners pertaining to the investigation of opioid deaths, and there's a corollary document that I'm spearheading that will be looking at standardizing the methodology that's used in toxicology labs, so the standards of practice are improving.

We need to encourage the use of the state PDMPs and maybe nationalize our PDMP eventually. I know there's effort for that or some interest in that; maybe I'm not sure effort yet. Looking towards the future, the CDC has put in place tens of millions of dollars to enhance the work that the medical examiners and coroners are doing for, for our people and for public health.

I think in the coming years, we are going to finally get specificity data down off of the death certificates, and that's going to help a lot. We're going to get enhanced testing done by the toxicology labs, and we're going to get increased timeliness, so the data from the CDC is going to be turned around, not in an instant, but targets are like 90 days to 120 days. So there will be much more real time and provisional data for people like you to work with. Thank you.

Clarifying Questions

DR. HERNANDEZ-DIAZ: Thank you.

Are there any clarifying questions for the speakers? If you can please direct questions to a specific presenter, and don't forget to say your name. Dr. Katzman?

DR. KATZMAN: I have a couple of questions for two different speakers if that's okay. The first is for Hilary Surratt, Dr. Surratt. First of all, thank you so much. Your presentation was unbelievably outstanding, so thank you. You're doing amazing work.

My first question is I just wanted to see what is your feeling -- you've had so much experience in so many parts of the country, but particularly referring to your work in Appalachian Kentucky, why do you think there are so few community members in Kentucky now misusing nonmedical prescription opiates compared to intravenous heroin, meth, and other illicit substances, compared to misusing prescription opiates the streets? Thank you.

DR. SURRATT: Sure. Thank you so much. My sense from interviews and surveys that we're doing in those communities is really that, largely, it's an availability issue. I think that's one of the primary things that I've learned. I think that the interventions at the state level have had a dramatic impact, comparable to the Florida type interventions that the last presenter just talked about.

Kentucky has implemented a series of initiatives as well that I know have had some impact in the street level availability of

prescription opioids. So I think that's clearly one of the issues. Then, of course, the scarcity of those drives the cost, which if you're familiar with Eastern Kentucky at all, it's a very impoverished area. There's a lot of other sorts of social problems, but cost is a major barrier for people as well. So even if there was some pill available, it's out of reach. It's been priced out of the market, so to speak, if that helps.

DR. KATZMAN: Thank you.

One more question, would that be okay? This is for Dr. Goldberger.

Dr. Goldberger, thank you so much. My question for you relates to towards the end of your slide, regarding the patients dying from multiple substances, not only prescription, or opiates, or IV heroin, but also for benzodiazepine, namely, alprazolam. We see that in New Mexico, alprazolam is right up there with IV heroin right now and meth. It's really the three: meth, heroin, and opiates.

My question is, regarding the number of

deaths in Florida, have you done any kind of dive into seeing if these patients that have died, have they been on medication-assisted treatments? Are they coming from opiate treatment programs or seeing their source of opiates? Thank you.

DR. GOLDBERG: No. Unfortunately, we have not, but that's a good point.

DR. KATZMAN: Thank you. Then I also think that we really need to discuss, perhaps tomorrow, the naloxone idea. Thank you.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Litman?

DR. LITMAN: This is Ron Litman.

Professor Surratt, I have a question for you, please. It concerns your slide with conclusions. They seemed a little bit contradictory to me. It seems that -- if you want to put it up; it's slide 50, 5-0. It seems to me that on one bullet point, you're saying that the highest doses of the pills were not necessarily sought after, but yet you're saying in the next bullet point that the demand would be high for

these high doses.

In my mind, I'm trying to think when we consider the whole picture today, how do we allow chronic pain patients to achieve their high doses, and at the same time, we have to worry about those being diverted. What's the relationship between the two? So I wasn't quite sure, if you could clarify.

DR. SURRATT: I'll do my best. it's a great question. I think in the data that I was presenting, first of all, one of the issues is that the data are imperfect, and a lot of the studies that I talked about, looking at dosage strength in particular was not one of the major points of emphasis. I was trying to piece together different pieces of information that would speak to it to some extent.

When I say in the second bullet about the demand for high dosage strength, that comes from the diversion study; in particular, the qualitative work with the dealers because they explicitly talked about those high dosage pills in the context

of obtaining those from pain clinics. So at that time, those south Florida pain clinics had standard prescriptions that they would write to anyone who came in, and it intended to be the 30-milligram immediate-release oxycodone combined with a benzodiazepine, and in large pill quantities.

So that was fairly organized, and for that reason, dealers were able to obtain those and then distribute them on the street. That's the one context where we really had some good information on that. But I guess my point in the first bullet -- and maybe it wasn't as articulate as it could have been -- is that in most of the studies, despite that point, what we saw among users was that they typically endorsed, as their primary opioid of misuse, a much lower dose tablet. So there is some lack of clarity around it. Hopefully, that's clarified.

DR. LITMAN: No. I think it's clear, but what I take away from that is that if higher doses were available, they would want them.

DR. SURRATT: Particularly for someone who is along the continuum to injection use for example, I would certainly say that there would be some desire or demand for that pill, among other things, yes. I don't think that that's an unreasonable assumption. We'd still have a lot of good data. I'm just trying to say that we need to weigh it around all the other factors that affect people's patterns of use and what they try to do.

DR. LITMAN: Thank you. I have one more question, please, for Dr. Cicero.

You gave us results of one of your studies, the questionnaire study, but that was mainly for patients who were checking themselves in for rehab.

DR. CICERO: Correct.

DR. LITMAN: How can you generalize that as a whole? There's got to be some inherent differences from those that do and those that don't go to rehab.

DR. CICERO: There probably are. It's always a limitation in our studies. We don't really have any data that would suggest that any

findings we're getting are unique. But yes, it's a treatment population of people usually motivated to get through this issue. Some of them are there by court order or family pressure, but a lot of these people are there because they really want to get better. So it's a unique population; no question.

DR. LITMAN: Thanks.

DR. HERNANDEZ-DIAZ: Thank you. Dr. McCann?

DR. McCANN: Mary Ellen McCann. I have a question for Dr. Goldberger and then maybe for Dr. Surratt.

Do you have a feeling for or do you know what age demographic dies the most, what the mortality rates are per age? When I look at Dr. Surratt's studies, the volunteers were in their late 30s, early 40s. Then there's anecdotal evidence of somebody getting narcotics for their wisdom teeth at age 18.

So is the journey 10 years, 15 years, 20 years typically? Does anybody have any data on that?

DR. GOLDBERGER: The CDC NCHS has data. I

don't have them with me prepared on the slide. You can also go to Florida FROST to see the Florida data, but those data are known. Typically, if I'm asked that question, I can say generally it does affect all demographics, from young to old, but we do see the middle age demographic affected more than the other age groups. But specific data for regions and for states, I would go to NCHS.

DR. McCANN: How about the onset of misusing these drugs?

DR. GOLDBERG: I don't have those data.

DR. McCANN: Thank you.

DR. HERNANDEZ-DIAZ: Dr. Mackey?

DR. MACKEY: Thank you. Two questions, please; one for Dr. Yarbrough and the second for Dr. Goldberger.

To Dr. Yarborough, can you bring up her last slide, please? First of all, I should comment that I really liked the way you were conceptualizing these pathways and the results you got. I think they are highly informative.

Here's my question for you. You put forward

5 pathways, of which we see 4 there. Can we just click it one more, the other way?

DR. YARBOROUGH: I think the last one is recreational.

DR. MACKEY: Yes, I was trying to get to that; one more. You've got it. Thank you.

When I'm looking this over, it really seems to me that what you have here are the first four of these are moderators or mediators, taking it from exposure to opioid-use disorder, where the last one is really the exposure, the exposure type. You got two exposure types. One is recreational and non-medical use and the other one is medical use. And it would seem that then both of those exposure types feed into those four separate pathways or mediators and moderators.

Is that a correct conceptualization or do you view those as five distinct and separate pathways?

DR. YARBOROUGH: No. I think you're correct, because we have multiple people describing multiple pathways, and you might enter by

recreational use, but maintain use because of emotional distress relief or something.

DR. MACKEY: Yes, because it seems like the recreational and non-medical feeds into these other four.

DR. YARBOROUGH: I think that's great.

DR. MACKEY: Okay, perfect. Thank you.

Dr. Goldberger, a fascinating discussion. I really learned a lot. Kratom, that seems to be in the news a lot. Any comments, wherever you are --

DR. GOLDBERGER: I'm right over here.

DR. MACKEY: -- perfect. What can you say about kratom?

DR. GOLDBERGER: Silly of me not to include that on this slide, particularly since we're here at the FDA. Kratom or mitragynine is a non-opioid, opioid-like compound. There is a lot of money now put into it in terms of researching the pharmacology and toxicology of it.

DR. HERNANDEZ-DIAZ: Sorry. I have to keep the discussion around the presentations. If this is relevant for you to understand the presentation,

that's fine, but I just have to say that the questions need to be focused on the presentation.

DR. MACKEY: I thought it might be relevant to the presentation in the context of substances that are identified in cause of death, and there have been concerns over kratom-related deaths in the U.S., and the fact that it is an opioid-like substance or a substance of potential abuse, I thought it was relevant. But I defer to you, of course.

DR. HERNANDEZ-DIAZ: Since the FDA ask not to include, I will defer to the FDA.

DR. STAFFA: This is Judy Staffa. I think it's obviously interesting, but I'm just having a hard time seeing how it's relevant to the high-dose opioid discussion. If you see that it is, then that's fine, but I'm not quite sure I'm following, but it may just be my ignorance.

DR. MACKEY: I think it's relevant, but I'll keep it short. One is it is an NPS drug. It is a drug that's been in the news. It is a drug that can result in death. But it is a drug also as a

kind of non-opioid drug, but drug with an opioid-like effect that is now being proposed to treat pain. I don't know if any physicians around here would even suggest that their patients would use it, but there are patients out there that are using it as a non-opioid analgesic; yes, as a replacement treatment.

DR. HERNANDEZ-DIAZ: Sorry for cutting the discussion.

Dr. Jowza?

DR. JOWZA: Thank you for the presentations. I have a question for Dr. Comer. It's actually pretty specific. It's about slide 16 that I needed clarification on. In that graphic, you have fentanyl, heroin, and oxycodone, and the mean peak likability rating, I suppose.

My question is regarding the oxycodone. It seems to me the doses are milligrams for a 70-kilogram person IV. So I wanted to clarify, is this IV oxycodone? And if so, what would be the oral conversion, since that's not something that's readily used here?

DR. COMER: All right. It's on a milligram per 70-kilogram basis because we wanted to adjust for body weight to control for that. It is definitely given IV. The oral to IV conversion is something I should know off the top of my head, but I can't remember at the moment, for oxycodone.

FEMALE VOICE: For IV? Ten milligrams of IV oxycodone is about 20 oral, but we don't have IV oxy in this country.

DR. JOWZA: Thank you. Can I ask one more question? This is for Dr. Surratt. I was just curious if during your surveys and studies, you found that there was, either on the patient side or on the dealer side, a preference for name brand medications versus the generics; if there was something behind it in terms of efficacy.

DR. SURRATT: That's an interesting question. I didn't report on it here, although we had a paper published several years ago sort of looking at branded versus generics, only because a lot of times when you're doing qualitative

work -- and maybe one of the other presenters has experienced the same thing -- people tend to express a preference for a brand name, a product name that they're familiar with; although in fact they tend to then call everything by that name.

It's hard to sort of distinguish. I have seen preference for branded products. In fact, we had a focus group in a methadone program -- it was not one of the studies that I reported on here -- specifically around this issue, where the clients or the users were absolutely adamant about the higher efficacy of the branded product versus the generic, and they gave a lot of talking and narrative around that point.

So I do see that. It's perceived that way. I think it relates to the fact that even street drugs are branded. Dealers will sort of brand their drug for recognition on the street and whatnot, so that you know, in a broad sense, what you're wanting to purchase when you're making street purchases. I feel that it's related to that.

DR. HERNANDEZ-DIAZ: Thank you.

Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. My question is for Dr. Yarborough. [Indiscernible - mic distortion]. Perhaps I'm just missing something. It seems like there's a contradiction between the inclusion criteria of two or more opioid-dependent diagnoses and the category of no problems. I'm assuming that the EHR data were entered by a physician, and the other [indiscernible] percent was just self-report, and that's why there's a contradiction.

DR. YARBOROUGH: They had to have two or more opioid=use disorder diagnoses just to rule out the possibility of having one being an error, but they didn't necessarily have to have it in the last year. So they may have had no problems with opioids in the last year, but qualified based on an opioid-use disorder diagnosis they received earlier.

DR. HIGGINS: Great. Thank you. One last question. This relates a little bit to

Dr. Mackey's question. I'm trying to discern any patterns to the pathways, and I'm wondering if you grouped the different segments of participants in your pie chart by the different pathways, or were they all just related to multiple pathways, and there's really no pattern.

DR. YARBOROUGH: We didn't do an analysis by the pie chart that you're looking at, and I would say just from knowing that data, multiple people were describing multiple pathways regardless of what you see in the pie chart there.

DR. HIGGINS: Okay. Thank you.

DR. HERNANDEZ-DIAZ: Thank you.

Mr. O'Brien?

MR. O'BRIEN: Yes, thank you. I've got about 10,000 questions, but I'll try to keep it to three. First, Dr. Goldberger, if I could ask from slide 11, you listed first opioids and alcohol, which I find very common among our patient community that that may be the first level.

The first question I had with that is, are there any objective data that shows what

combination dosage of opioid and alcohol could be a death-related issue?

DR. GOLDBERGER: No, there's no data.

MR. O'BRIEN: Secondly, with that, on slide 13, you listed all of the drug caused deaths in Florida, but I noticed alcohol is not listed on there as one of the drugs.

DR. GOLDBERGER: That wasn't on purpose. We just compiled the slide, and it was by drug. I know alcohol's a drug, but those data are available on the FROST website.

MR. O'BRIEN: All right. Thank you.

DR. GOLDBERGER: Sorry.

MR. O'BRIEN: No, that's okay.

My second question is for Dr. Yarborough. My first question of Dr. Yarborough is, can I just ask what year this study was done?

DR. YARBOROUGH: Yes, let me just look. I thought I might get that question. I'm looking in our paper and not finding it quickly. Can I bring it up for a minute?

MR. O'BRIEN: The only reason I asked the

question is I found it curious in looking at your pathways and your descriptions that were there leading up to it, first of all, there's no alcohol measured in there despite the listing in Dr. Goldberger's study and what his findings are. Also, the amount of drugs that are available and the ability to switch and take more, et cetera, especially in the last several years with the onset of policies in the states, I think most well-managed patients know that today's surplus is tomorrow shortage.

So they're more worried about making sure they can manage their pain, and I think also that's one of the policies that's happened over the last seven years. We've shifted the management to the patient because the patient wants to make sure they have the amount of drugs they need to take care of themselves, so they're being more diligent in terms of not letting that out. It's not as readily available to divert to other people, et cetera, et cetera.

So I was just curious with that in terms of

your availability. That's why I was asking the date of when this was actually done.

DR. YARBOROUGH: Let me find that, and I'll let you know.

MR. O'BRIEN: Thank you.

DR. HERNANDEZ-DIAZ: Thank you.

Dr. Marshall?

DR. MARSHALL: Brandon Marshall, Brown, School of Public Health. I have a question for Dr. Surratt. I enjoyed your presentation. The question is about the high prevalence of non-prescribed buprenorphine use among SSP participants. I just wanted to confirm that it's injection of buprenorphine, and if so, if any information was collected on what product of buprenorphine?

I assume if it was suboxone, I was just wondering if you had any knowledge of what participants were doing to overcome the antagonist effects of the co-formulated naloxone.

DR. SURRATT: Yes, thank you. The data that I presented with, I think from memory, the 25.8

percent that reported --

DR. MARSHALL: Yes, slide 44.

DR. SURRATT: -- that was specifically injection in the past month. So we also asked about non-injection use, so it is much higher. So people are using by different routes of administration, and that 25.8 percent was injection.

I don't have a lot of great information around how they're overcoming it, but I have users in the qualitative repeatedly say -- from injecting, and suboxone is the product that I'm aware of -- that it immediately sort of normalizes them. It's not euphoric or anything like that. It's just a balancing
out effect that they typically report. In terms of practice about how they might be overcoming the naloxone, I'm sorry that I don't have better information for you.

DR. MARSHALL: [Inaudible - off mic].

DR. COMER: That's a really good question that you have. We did a series of studies to

examine injection and intranasal use of buprenorphine-naloxone combinations in the lab setting like I described earlier today. What happens is that if people are physically dependent on buprenorphine, the naloxone and the suboxone that's available now therapeutically is enough to kind of blunt the initial euphoric effects that are provided by the buprenorphine, but not enough to precipitate withdrawal. So they just have to wait for half an hour to an hour, and then they'll get the good drug effects that they're looking for.

DR. HERNANDEZ-DIAZ: Thank you.

Dr. Sprintz?

DR. SPRINTZ: Hi. Michael Sprintz. My first question actually is for Dr. Comer. On slide 11 when you're talking about a drug versus money choice, I was wondering did you consider that the drug that you -- you talked about they'd get a tenth of a drug versus $2. Did you consider what their drug of choice was and the cost for them to buy that on the street as part of their decision process in choosing?

DR. COMER: The drug of choice at the time we ran this study, they were all primarily heroin users. Prescription opioids were not -- I mean, they were around, but the group that I was studying were heroin users. We gave all of the drugs that we tested under double-blind conditions and in randomized order, so they had no idea what drug was being administered or anything.

So they were responding just purely to what drug effect that they got. In that way, I think we were really careful to get a good handle on what drug liking looks like, how much they would be willing to pay for it, and that kind of thing.

DR. SPRINTZ: So they'd be comparing it to whatever they're used to --

DR. COMER: Yes.

DR. SPRINTZ: -- and then figuring that out in their head as they're making those decisions.

DR. COMER: Yes. You're asking a good question. I think one of the other speakers earlier today kind of touched on this as well, that people do really pay attention to these subtle

differences in drug effects. Morphine, for example, produces a pretty strong histamine response, and they really don't like that very much.

We use this procedure most often because it's straightforward to us, and it's a little bit kind of weird for somebody who's not used to looking at this. But another procedure that we've used is a drug-versus-drug procedure. We give them a sample of dose A and then another sample of dose B, and we ask them which one would you prefer to try to kind of tease apart these really subtle differences.

The way I like to think about it is opioid users are kind of like people who love wine or who love brandy. They can tell these subtle differences in each of these kinds of drugs.

DR. SPRINTZ: Absolutely, yes. On slide 25, you showed that buprenorphine was not self-dministered at all, at any dose. My question was, you said two things; one that they went into withdrawal if they took too high a dose. Were they

taking other opioids at the time. And the other question is, did they have a choice of which drug to self-administer?

DR COMER: Yes. Yeah. In this study, we maintained everybody on morphine, so we were trying to mimic kind of the typical pattern of heroin use on the street. So we gave a 30 milligrams QID8 using a roughly 4-to-6 hour interdose interval, which is what they do on the street. Under these conditions, buprenorphine was making them sick.

DR. SPRINTZ: Yes, that's important, because it's not that people won't self-administer buprenorphine; it's that if you're already taking something regularly, you don't.

DR. COMER: Exactly. And that's what I showed in the buprenorphine versus methadone study, where we detoxed them first, so they were not physically dependent. They took a lot of buprenorphine. And as I just mentioned to one of the other panel members, when they're physically dependent on buprenorphine, buprenorphine itself produces -- because we did that study as well. We

directly compared it to heroin IV, and it was indistinguishable. They really liked the buprenorphine alone.

DR. SPRINTZ: Wow. That's important. Thank you.

I had one quick question for Dr. Surratt. Did you guys look at abuse-deterrent formulations?

DR. SURRATT: That was not a focus of any of the studies that I presented, so unfortunately I don't have any good information on that.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Boudreau?

DR. BOUDREAU: Hi. Denise Boudreau. Thank you for great presentations. My question is for Dr. Cicero. Fascinating data on these patients entering the treatment facility. My question is two-part. Do you have information on the mean/median daily dose of the patients entering the facilities? I'm wondering if perhaps that explains some of the differences that you see by the IR opioids versus the ER/LAs. And I'm particularly referring to slide 34 and 35, where you see

differences by those two groups.

The second part of that question is also related to dose, if that could somewhat explain, among the oral users, depending on what their dose is, if they're high, low, medium, their preference for staying on oral therapies versus using other formulations.

DR. CICERO: We have the data, but I don't recall the exact numbers right now for you. Sorry. I can get that to you.

DR. BOUDREAU: Do you know a sense of -- if the ER/LA users were very much higher than the IR users?

DR. CICERO: They were, yes. In response to one of the earlier questions, too, a lot of our people started out with alcohol at a very early age, 8 or 9, then they actually go to marijuana after that. But if you're looking at gateway drugs, alcohol seems to be it, at least in our population.

DR. BOUDREAU: Thank you.

DR. HERNANDEZ-DIAZ: Thank you. Last

question from Dr. Hummel.

DR. HUMMEL: Hi. My question is for Dr. Goldberger. Keeping in the context of this meeting and hearing stories from Ms. Farrell, I was wondering if you could speak to the issue of risk and the likelihood of accidental overdose in patients that are monitored by physicians.

How often do you -- is it an issue for patients that are -- what's the likelihood of overdose and safety concern in patients that are properly monitored by physicians that are on high-dose opioids?

DR. GOLDBERG: I'm not a clinician, so I can't really answer that question for you. My patients are decedents. But I'm going to pass the microphone.

DR. SURRATT: I wasn't addressing that point, but I have one that I wanted to clarify on my last statement --

DR. HERNANDEZ-DIAZ: From your presentation?

DR. SURRATT: -- if that's okay.

DR. HERNANDEZ-DIAZ: If it relates to the

question.

DR. SURRATT: This is related to the last question that was asked about buprenorphine. I'm sorry. I just wanted to clarify that the data that I was describing was with buprenorphine and heroin producing lots of good drug effects and liking when they're maintained on buprenorphine.

We tested under conditions, under trough conditions, of sublingual buprenorphine maintenance. So I don't want to leave the impression that buprenorphine and heroin are producing these tremendous effects when people are physically dependent on buprenorphine in general. It really depends on -- sort of like when people are maintained on methadone, they wait until 23 hours before they use a heroin dose because the methadone is at trough levels. And that's when I studied the effects of IV bup and IV heroin.

DR. HERNANDEZ-DIAZ: Thank you.

This will be the last questions for the speakers because Dr. Yarborough is leaving. So if anybody has a question for her, it has to be now.

If not, we can take a break.

DR. SURRATT: I did find the dates. The recruitment period for that study was 2006 to 2009.

DR. HERNANDEZ-DIAZ: It's a continuation of that? Very last comment.

MR. O'BRIEN: Sorry. It's just a follow-up, really, to the question that really hasn't been answered, and I'll ask it in a different way. This series of studies that we looked at this afternoon -- and anybody can answer this, I suppose, any of the speakers. This whole series was coming from the perspective of those that are seeking treatment or those that are known to have abuse, or disorders, or misuse, et cetera, et cetera.

So the question is, what percentage of the total population does that actually represent? I would ask a second question then. I would like to know, do we have any large studies of the tens of millions of well-managed chronic pain patients in terms of what is keeping them from being along the pathway of misuse or abuse, and looking at it from

a different perspective? Are there studies like that rather than looking from the perspective --

I understand the reason they're doing it from bottom-up, but I'm asking from top-down, do we have any large studies that would tell us why do people not follow this pathway? Why is it that we do have the majority of those that are, in fact, managing their pain well?

DR. HERTZ: This is Sharon Hertz. That's not a clarifying question. That's asking for additional information that hasn't been presented, and I'm going to say we leave that for discussion.

DR. HERNANDEZ-DIAZ: Thank you. We'll save it for the discussion.

We will now take a 15-minute break. Panel members, please remember that there shall be no discussion of the meeting topics during the break among ourselves or with any member of the audience. We'll come back at 3:45.

(Whereupon, at 3:30 p.m., a recess was taken.)

DR. HERNANDEZ-DIAZ: We'll continue with the

speaker presentations with Dr. Sandbrink.

Guest Speaker Presentation - Friedhelm Sandbrink

DR. SANDBRINK: Good afternoon. First of all, thank you for giving us the opportunity to talk, for me to give the opportunity to talk about the experience of the VA. For me as a background, I'm a neurologist and pain physician. I've been with the VA since 2001. I lead the Pain Rehabilitation Program, the pain program at the Washington DC VA Medical Center, but most of my time is now spent as the national program director for pain management for the Veterans Health Administration.

I really want to thank the FDA for organizing this, as well as giving us the opportunity to give our perspective and report on our experience with our opioid safety initiative.

I'm going to give you a little background in regard to the Veterans Health Administration and the pain and opioid situation there and talk about the VA opioid safety initiative, in particular, highlight our approach in regard to opioid

prescribing as it's outlined in the VA DoD clinical practice guideline; talk about what is our guidance in regard to opioid tapering as well as risk mitigation strategies; and some of our analysis, early analysis, not all published yet, in regard to predictive modeling of overdose deaths and suicide deaths.

Just a little bit of a background, it's known that in veterans, pain is more common, and when it happens, it tends to be more complex and often more severe. You see data here. I'm not going to read you the data. On the right side, that is data that isn't published, but this specifically looks at veterans in the Veterans Health Administration receiving primary care from the VA. As you can see, 1 in 3 is a chronic pain diagnosis, 1 in 5 is persistent pain, and 1 in 10 is severe persistent pain.

When we compare the data from 2008 to 2015 over time, the trend, we actually see that pain severity and pain scores actually gradually have increased over the years, as well as the prevalence

of mental health diagnosis, whereas common medical diagnosis such as diabetes, heart disease, cancer has been stable.

Clearly, when pain occurs, it's often in the setting of mental health comorbidities and results in high impact pain. We truly, at least for the VA, have to address pain, medical, and mental health conditions in conjunction. As you can see, we list pain management and opioid safety in our foundational services, and the integration across service lines is something that we strongly emphasize.

I want to mention just briefly that the most frequently identified risk factor among veterans who died by suicide is pain. Whenever we analyze the behavioral heart autopsy reports, pain is a major factor for that, and often it is quoted that veterans are at higher risk for harms from accidental poisoning. I show here Dr. Bohnert's study, and I'll show you a little bit more about that, that truly shows that on a population basis, the risk of an overdose death for veterans is

higher than in the non-veteran U.S. population.

We've talked a lot this morning already about the association between high dosage or dosage increases and overdose death as well as suicide. Here, this is data for the VA. The first one is, again, the Bohnert study that we've talked about earlier today. And clearly, there is a correlation. The higher the dosage is, it's about a factor of 7 for patients who are above 100 milligrams of morphine equivalent.

Just a little bit of explanation for this -- and I pulled out this somewhat old slide of mine that shows that, yes, if you look at the rate here above 100 milligrams of morphine equivalent, the overdose deaths, those were 125 patients and had a ratio per 1000 person of 1.24, about 7 times greater for the reference here.

On the other hand, out of the 606 patients who had chronic non-cancer pain and deaths in this series, only in quote, obviously, "125 were in this high dosage ratio." The majority were actually not on an opioid medication or, in conjunction, were on

lower opioid dosages.

Similarly, this study by Dr. Ilgen, that was mentioned also earlier today about the opioid dose and risk of suicide, shows that while with higher doses the risk goes up, it is not clear that the opioid medication in itself is a factor, but rather the high-dose opioid prescribing may be a marker for other factors drive suicide.

This is a study by Dr. Bohnert that looked at this a little bit later, looked at this again, but in a more recent study. It really shows that there is a great overlap in regard to patients who have overdose deaths as well as patients who don't have an overdose death in regard to the dosage. These are veterans being treated with opioid medication.

As you can tell, if you just concentrated on the high-dose opioid therapy patients, you would certainly miss the majority of patients. The median doses were 60 milligrams of morphine equivalent. Half of the patients who died had, obviously, a dosage below the median.

I'm going to tell you a little bit on how do we approach the Opioid Safety Initiative in the VA. This was implemented nationally in 2013 after it was piloted in a few areas in the VA in 2012. The goal of the Opioid Safety Initiative is truly to reduce a reliance on opioid analgesic, but it's not the medication itself that is the emphasis. It really is about providing better access to pain care that reduces the reliance on opioid medication by doing a more comprehensive pain approach.

As you can see, access to non-pharmacological modalities is really integrated into this, as well as education. One of the issues that we did, we established the OSI dashboard that makes opioid prescribing very visible within the VA system, and it was tied in initially with a request of the facilities to specifically review the situation of the patients who are on the highest opioid prescribing dosages.

A couple of years later, in 2017, we issued the VA DoD Clinical Practice Guidelines; those are all publicly available. The one for opioid therapy

was published in early 2017, a little bit less than a year after the CDC guidelines. There are a lot of similarities, but I'm just going to give you a little bit information about it because this drives our teaching for our VA practitioners.

The first recommendation in there is we recommend against initiation of long-term opioid therapy. The emphasis is actually -- and this is my personal emphasis -- both on initiation as well as long-term opioid therapy. We are not saying you shouldn't start somebody temporarily on an opioid medication. We are not saying that somebody on opioid therapy already must be taken off. This is not in the sentence. Rather, it is that you should start out with non-opioid approaches first, including non-pharmacological approaches.

In regard to the initiation of continuation of opioids, it specifically recommends against opioid therapy or initiation of opioid therapy in patients who are young, less than 30 years of age, realizing there is a higher risk of opioid-use disorder in the younger population or a higher risk

for that.

Risk mitigation strategies, I think we all agree about those. Assessment for suicide risk was integrated into our recommendations and close follow-up as well. In regard to the patients who are already on opioid medication, it was very clear that there is not, or at that time, an evidence-based suggestion that we could pull from the literature about what's the best tapering approach. So our recommendation is to individualize this for each patient. Clearly, the recommendations is to avoid sudden reductions. If you taper because the risk is greater than benefit, you should do it very slowly.

These are the parameters that we routinely monitor in the VA system, and the feedback about these parameters is provided back to the facilities and the practitioners. The first parameter we've consistently followed since 2013, so everybody is available about the prescribing of the facilities.

I think the attention to the factor itself, although you may not make a specific recommendation

in regard to dosages, it's already what drives practitioner's behavior. What we follow, though, in regard to policy -- you see this with dates associated with that. We have a policy for informed consent, PDMP checks, as well as opioid safety risk reviews that I will outline a little bit more.

This is the result of this. We've reduced opioid prescribing overall since our peak in 2012, at the end of the fiscal year 2012, by more than 50 percent in regard to overall opioid prescribing. I should say this does not include tramadol. The reason for that is because at that time when we started the Opioid Safety Initiative, tramadol was classified differently than it is today. And in order to maintain continuity of data, at least in this data set, tramadol is not included. We obviously can get the data with tramadol as well.

As you can see, reductions are more than 50 percent overall in all opioid prescribing. But if you look at the specific categories where we have concerns, opioid and benzo prescribing has been

reduced by more than 80 percent. Long-term opioid prescribing has reduced by 58 percent and high-dose opioid prescribing actually is reduced by 70 percent.

Now, I'm going to give you this one here, this small slide up there on the right-hand corner. It really shows that even in regard to high-dose opioid prescribing, but as well as in opioid prescribing, we're still much higher than compared to 2003 when we started our observation.

I should say that for all of opioid prescribing. In the high-dose opioid prescribing, though, we've made great reductions. I just put last night the latest number for that. At the peak of opioid prescribing for high-dose opioids, in 2011, we had 5,237 patients on more than 400 milligrams of morphine equivalent, and as of quarter 2019, we have 694, so that's an 87 percent reduction.

For the 300 to 400 milligrams group, we have now 874 patients on this, which is an 85 percent reduction. On the 200 to 300 milligrams dosage

range, we have now 2,470 patients, which is an 80 percent reduction, and for 100 to 200 milligrams, we have now 12,207 patients, which is a 67 percent reduction. In overall high-dose opioid prescribing, about 400 milligrams of morphine equivalent has reduced by about 70 percent overall, and as I'm pointed out, in particular, in the very high dosage range.

Interestingly, the reduction of these high-dose opioid patients started before we actually initiated our Opioid Safety Initiative. The peak of the very high-dose opioid prescribing was in 2011, and our Opioid Safety Initiative went live in 2013.

Now, where is this reduction coming from? Here is one slide only from the Hadlandsmyth study that was published a good year ago, where she showed that 83 percent of the reduction in opioid prescribing in the VA is actually because of the reductions of long-term opioid prescribing, and more than 90 percent is because we do not initiate, typically, long-term opioid therapy.

They showed very clearly that if you look at the patients who are being started newly on long-term opioid therapy and the attrition rate, patients who are exiting long-term opioid therapy, the exiting has been more or less stable, but there's such great reduction in starting patients newly or converting them from a temporary into a long-term opioid prescribing situation.

I have two slides about opioid tapering, and I'm bringing these here because this is the guidance, and I pulled this study from -- these are studies that are 2 years old. They were issued together with our opioid taper decision tool. So this is really what is the teaching in the VA and has been the teaching in the VA for the last couple of years.

Mostly, as you can see on the slide, we emphasize that if you make reductions, tapering should be done very slowly. It should be patient-centered, and our guidance has been about 5 to 20 percent every 4 weeks, but individualized to each patient; clearly warning against sudden

reductions and making sure that patients have a very close follow-up.

It's very important to realize that you have to get the patient on board with this. This takes time, and we need to give providers and patients time to engage their patient, to motivate them, so this becomes a collaborative approach. That is really the emphasis, that it is patient-centered, and we do not have any specific guidance in regard to certain dosage levels that must be achieved for a particular patient. We caution against involuntary tapers because there's a significantly greater risk that we feel is associated with that.

Here are two slides about more recent data that was just published, I should say, in regard to overdose deaths in veterans that very closely mimic the data from the CDC. This was just published about two weeks ago online. As you can see from 2010 to 2016, there has been a gradual increase in regard to overdose deaths from opioids in general, but this is specifically in regard to the increases from heroin, as well as from synthetic opioids

other than methadone; whereas prescription opioid medication-related overdose deaths have been stable, and in the last couple of years are actually gradually coming down.

The most recent data we have is for veterans from 2016. We get it delayed from the CDC, that identification, specifically looking about the patients who had an overdose death, how many of those actually had a receipt of an opioid prescription in the last 12 months and 3 months.

You can see that, over time, this clearly has been a smaller percentage of these patients. In particular in the last two years, after the implementation of the Opioid Safety Initiative, since 2014, we have seen a rather significant reduction of prescription opioid medications having been issued in the last 12 months prior to these deaths.

A few studies from the VA just very briefly. I'm going to skip this. Lovejoy looked at the reasons for this continuation in patients on long-term opioids there. The reality is that often

it is physician initiated, provider initiated, rather than patient initiated, often due to aberrant behavior. But even in the same data set, after following these patients over time, they actually showed that the pain intensity of these patients does not increase as an aggregate. Patients who have low to moderate pain severity, actually after opioid discontinuations, had slight reductions in regard to their pain severity recorded.

Nevertheless, we know that in these patients, suicidal ideation and suicidal self-directed violence is common, as is shown here. Obviously, the numbers are small, but we are concerned about each and every veteran in this regard and need to minimize and mitigate this completely.

I'm going to show you in the next 5 slides some data that isn't published yet, which comes from Jodie Trafton and her group, from the Office of Mental Health and Suicide Prevention, the Performance Evaluation and Resource Center, the

PERC in Palo Alto, and appreciate the ability to show these data.

This looks at the fiscal year 2013 patients who had an opioid medication, who by the end of fiscal year 2014 had either overdose deaths or had a completed suicide death, had a completed suicide. As you can see here, the dosage range is really across the whole spectrum.

If we just concentrated on the high-dose opioid therapy, that would be only about 15 to 20 percent of the patient; 85 percent are below the 90 milligrams of morphine equivalent. But the majority of those have mental health and a substance-use disorder diagnosis, and that's across the spectrum.

Yes, for an individual patient who is on high-dose opioid therapy, the risk is significantly increased. If you look at the population base, the vast majority of patient experience in overdose deaths will be not in the high-dose category because they are the vast majority of patients who have low opioid medication, which isn't in itself

completely safe.

If you look at the risks for the overdose that are related, and we can see what are the past risk factors, psychiatric comorbidities is certainly what drives this, including substance-use disorder diagnosis, as well as past admissions, for instance, in mental health treatment programs. Medical comorbidities are much lower in regard to risk. Benzodiazepine as a risk factor of 1.4, as you can see, much lower than the diagnosis of mental health in itself.

This is a study that looks at the same data and looked 5 years back to when did these patients get started on opioids, and if they had an overdose death, what was the timing -- or if they had a death, what was the timing in regard to either opioid initiation or opioid discontinuation?

What we can find here -- and we did this in 2 data sets in the fiscal year 2010, as [indiscernible] said, we find that after opioid cessation, after stopping opioid medication, or after opioids were not continued, for the next 3 to

6 months, there's a significantly increased risk for an overdose death or suicide. We find a similar risk after initiating opioid therapy, but the risk is actually higher with discontinuation than with initiation.

You see this here on the slide, especially in fiscal year 2013, if I look at the hazard ratio, opioid cessation in itself has a ratio of about 3 to 4 times. I should say this is an observational analysis here. This is not a prospective study. This is for all opioid prescribing, so it really is an aggregate for it.

You can also see that long-acting opioid medication is more risky or have higher risk than short-acting medication, as it's been told here. The opioid dosage in itself has a relatively small factor. For example, 120 milligrams of morphine equivalent daily dosage has about the same risk in our model as having a diagnosis of PTSD, or as having a diagnosis of an alcohol-use disorder. It's so important to look not just at the opioid prescription, but look at the person who receives

that prescription, so that is our emphasis.

Also, benzodiazepines are listed here, but also keep in mind that other sedating medications are also very relevant in this context. The more sedating -- even evidence-based medication for pain, including antidepressants, anticonvulsants, seem to contribute to risk at least from an observational standpoint.

This is a dashboard that we used to analyze all patients and provide the data back to our providers; just a little bit of information, which really comes out of it. I could speak to all of these, but in the interest of time, I just want to mention these.

It really leads us away from looking at a prescription, but rather looking at each and every person individually, and trying to address risks in this regard; suicide safety planning, routine screening for all patients who are in pain clinics for the suicidal ideation; and overdose education and naloxone distribution, which is done routinely for patients in any patient where we think there

may be at risk and not tied to a dosage above 50 milligrams. We emphasize also to give it to patients who have been stopped on opioids or may be at risk for relapsing in some ways with opioid-use disorder.

Obviously, access to medication assisted treatment for opioid-use disorder, addressing mental health disorders, pain management teams at all facilities that can support providers as well as their patients; and improved care coordination. We do have risk review teams at each facility that review every patient that is felt to be, based on our dashboard, at the highest risk for an overdose or for a suicide; and to bring in all team members -- mental health, primary care, pain clinics, and other team members -- to work together to try to coordinate care; not to change necessarily the prescription, but truly to coordinate care across the service lines.

This is my summary here for our Opioid Safety Initiative. Clearly, what we know is that the risk of prescription of opioids is correlated

with dos age and duration and co-prescribing with other sedating medications. We feel that at least for veterans, mental health conditions, substance-use disorder, and other conditions contribute greatly to the risk.

The VA DoD Clinical Practice Guidelines recommends initiation of long-term opioid therapy, but does not mandate a reduction of patients below a certain level across the board. Opioid risk mitigation strategies have priority in regard to, I think, adjustments to the prescription itself, so PDMP checks, urine drug screening, informed consent, education of every patient on long-term opioid therapy, and then close follow-up.

Just briefly, when patients are discontinued on opioid medication, one way why maybe the risk is increased is because they don't have that follow-up anymore. You don't need to see the provider in 4 weeks again. Suddenly this natural link, the contact to the pain clinic or to your primary care may be interrupted.

The other thing is that both providers and

patients need to be aware that there is this protective withdrawal syndrome, and patients may be at risk for restarting opioids a few months later when the tolerance is so much lower. Therefore, it is very important to maintain the contact during this 3 to 6-month period after maybe an opioid medication has been significantly reduced, and certainly after it has been also discontinued.

As I said already, opioid dosage reductions have to be very patient-centered. Clearly, if somebody has an opioid-use disorder, which may manifest during these adjustments of the pain medication, then, clearly, access has to be provided to evidence-based therapy, MAT [ph]. Thank you.

DR. HERNANDEZ-DIAZ: Thank you, Dr. Sandbrink.

We will now continue with another guest speaker presentation with Dr. Michael Von Korff.

Guest Speaker Presentation - Michael Von Korff

DR. VON KORFF: I'm going to be talking about management of chronic opioid therapy in

primary care settings. So I'm not talking about hospice care, really palliative care; I'm talking about management of common chronic pain conditions with opioids in primary care settings.

Well, why primary care? Primary care is where most people with chronic pain are managed, and it's where most opioids are prescribed. By way of context, the United States prescribes 4 times the defined daily doses that they do in many other European countries.

The evaluation that I'm going to show you as sort of a thought question, if you took prescribing standards for opioids in Denmark, or Netherlands, or Scandinavia, generally, or France, and implanted them in the United States, or if a healthcare organization wanted to go in the direction of prescribing opioids the way they do in other countries that have high standards of care, in what ways is that going to help patients, in what ways is that going to harm patients, and in what ways is it not going to make a difference one way or another?

I'm going to describe key results of evaluation of a healthcare organization's initiatives to reduce risks among persons receiving chronic opioid therapy, which I'll call COT, so I don't have to say it 52 times. This research was funded by the Patient Outcomes Research Institute. We had a great advisory panel. Marianne Farrell was one of our advisors.

We had patient advisors on the full gamut, from people that were really active in trying to reduce opioid prescribing to people that were very favorable towards opioid prescribing. They really got along very well and had very little trouble reaching consensus and giving us advice on the study. I think we as professionals maybe could learn something from that.

I'll describe the health plans, opioid risk-reduction initiatives amongst COT patients and our evaluation methods, and then I'm going to show what changes in prescribing and management resulted from implementation of these initiatives. Then I'm going to compare what happened to opioid overdose

rates and what happened to patient-reported outcomes between chronic opioid therapy patients and intervention clinics that implemented initiatives and control clinics that didn't.

Group health, a Washington state health plan that is now part of Kaiser Permanente, sought to reduce opioid risks among chronic opioid therapy patients through two risk-reduction initiatives.

Starting in 2008, Group Health sought to reduce high-dose opioid prescribing in response to a Washington state guideline that recommended avoiding doses above 120 milligrams morphine equivalent. Then in the fall of 2010, Group health implemented multifaceted risk stratification and monitoring initiatives in response to Washington State legislation that established chronic opioid therapy management guidelines, as a matter of state law.

These initiatives were implemented in the health plan's 26 integrated group practice clinics but not in clinics providing care on a contract basis to similar group health enrollees, so let me

describe these initiatives.

The dose-reduction initiative sought to keep opioid doses as low as possible by avoiding dose escalation and by tapering patients to lower doses when clinically appropriate. These kinds of guidelines are not an edict. They respect the relationship between doctors and patients, but they do create a clinical context in which there's transparency, in which a medical director or clinic is looking at how his or her physicians are prescribing, and providing supervision when somebody's prescribing doesn't seem to be in accord with the direction that seems clinically appropriate.

The risk stratification and monitoring initiative designated a single clinician for managing each COT patient. A COT care plan was developed and placed in the electronic medical record. Standards were set for the frequency of urine drug screening and monitoring visits based on patient risk level.

Over 80 percent of primary care physicians

completed an online training program, which took about 45 minutes. It was an online program initially developed by the VA, which was quite good. That was followed by clinic staff meetings to discuss the implementation of standards for COT management.

The evaluation design was a natural experiment in which we compared trends among patients from the intervention clinics that implemented these risk-reduction initiatives to patients from the control clinics that did not. Over a 9-year study period -- we're using retrospective data; we didn't have 9 years to do the study -- we compare process and outcome trends among 22,673 COT patients from the intervention clinics and 8,469 COT patients from the control clinics. We used interrupted time series methods to compare trends in opioid prescribing and opioid overdose.

In our evaluation, we defined chronic opioid therapy as receiving at least 60 days supply of opioids in a 90-day period. In 2014 and '15, after

the initiatives had been sustained in the intervention clinics for many years, we interviewed 935 COT patients from the intervention clinics and 653 patients from the control clinics to see if there are differences in pain outcomes, perceptions of patient care, and the prevalence of prescription opioid-use disorder.

The baseline phase of the evaluation was 2006 through 2007. The opioid dose-reduction phase was 2008 through September 2010. The risk stratification and monitoring phase was October 2010 until the end of the study in 2014.

Trends in opioid prescribing and in opioid overdose were monitored from 2006 through 2014 using electronic healthcare data for non-fatal opioid overdose and state death certificate data for fatal overdose. The survey of chronic opioid therapy patients from the intervention and control clinics was carried out in 2014 and 2015.

I'll first describe changes in opioid prescribing and management amongst COT patients. Over the evaluation period, the number of persons

and the percent of the adult population receiving COT continued to increase in both intervention and control clinics until 2012 when the numbers began to level off. By 2012, almost 3 percent of adults were receiving chronic opioid therapy in any given quarter.

During the dose-reduction phase, we found that reductions in opioid dose were substantially greater in the intervention clinics than in the control clinics. Doses started to diverge in 2008. Differences in dosing trends emerged that were both clinically and statistically significant.

After the dose-reduction initiative, patients in intervention clinics were being managed on doses that averaged almost 20 milligrams a day lower than patients in the control clinics. Differences in dose were sustained through 2014, but the intervention control differences in dose did not increase in size during the risk stratification and monitoring phase.

The percent of COT patients on high opioid doses, above 120 milligrams morphine equivalents,

as defined by the state guideline, showed a similar pattern. The percent on high doses dropped during the dose-reduction phase in the intervention clinics but not in the control clinics. After the dose-reduction phase, the percent on high opioid doses in the intervention clinics was about half that of COT patients in the control clinics.

Neither the dose-reduction nor the risk stratification and monitoring initiative targeted reduction in co-prescribing of sedatives. The percent of COT patients with concurrent chronic use of sedatives increased somewhat in the control clinics from 2010 through '14, while remaining unchanged in the intervention clinics. About one third of COT patients were concurrently using sedatives on a regular basis, and this has been found in many other studies. It's very common.

The percent of patients with a COT care plan in their electronic record increased rapidly to over 80 percent of patients in the intervention clinic starting in October 2010. It was not possible to determine the percent of patients with

COT care plans in the control clinics. The percent of COT patients in the intervention clinics receiving a urine drug test at least once a year also increased rapidly to about 50 percent per year starting in October 2010. This trend was relatively flat in the control clinics.

If you look, there was a question about the quality of care for COT patients. I think, in general, if you look at the control series, what is it, about 10 percent are getting a urine drug test in a year. That reflects community practice. If you looked at other indicators that people would consider sort of basic standards, for management of drugs that are inherently unsafe, this is what you'd see.

Group Health I think did a pretty good job in getting urine drug testing up to 50 percent, but the state guideline was that all patients should have it every year. The VA, which really knows how to do things, they got up to 80 percent. That's incredible. But this idea that chronic opioid therapy patients are closely monitored and that

they're screened for risk before the therapy is initiated, that's a fantasy. It doesn't happen in primary care. I don't know if it happens in pain clinics either because there isn't much research there, but it certainly does not happen in primary care.

So you have very dangerous drugs being prescribed and managed under very lax conditions, and that really has to be remembered when we talk about chronic opioid therapy.

Now let's look at what happened to opioid overdose rates following these changes in patient care. During the dose-reduction phase, we found a statistically significant drop in opioid overdose rates in the intervention clinics. This is among COT patients. From 2007 to 2010, the rate of fatal and non-fatal opioid overdoses dropped by about one-third among COT patients in the intervention clinics to about 4 overdoses per 1000 patients per year. This is fatal and non-fatal.

There was no further reduction in overdose rates during the risk stratification and monitoring

phase in the intervention clinics. However, the rate of decline in opioid overdose rates in the intervention clinics did not differ significantly when compared to the change in overdose rates in the control clinics. Thus, our evaluation results were inconclusive for whether dose reduction was associated with reductions in overdose rates. Rates drop within intervention clinics, but the rate reduction was not significantly greater than in the control clinics.

Since the number of COT patients in the control clinics was about one-third the number in the intervention clinics, statistical power to detect between group differences in overdose rate changes was limited. This inconclusive result I think could be resolved pretty quickly by seeing what's happened in the VA or looking at experience more recently in a large Kaiser plans that have dropped doses more than we did back 10 years ago.

We looked at where the reduction in dose in the intervention and control clinics fell on the dose-response curve for overdose risk. We found

that dose reductions achieved in the intervention clinics were not on a steep part of the dose-reduction curve. They were close but not quite there. And really, if you think that dose-response curve is accurate, you'd like to be getting doses down below 30 milligrams, and we didn't get average doses that low. This may explain, in part, why larger reductions in overdose rates were not achieved.

Now let's return to patient-reported outcomes. COT patients from intervention and control clinics were interviewed in 2014 and '15 after the dose-reduction and the risk stratification and monitoring initiatives had been implemented in the intervention clinics for at least 4 years.

We assessed pain intensity and pain-related interference with activities using items from the PEG scale. We saw no differences in pain intensity ratings among COT patients between intervention clinics that had lowered opioid doses and control clinics that had not.

Most COT patients in both settings rated their pain intensity in the moderate to severe range. We also saw no differences in ratings of pain-related interference with life activities. The large majority of COT patients in both intervention and control clinics rated pain-related interference with life activities in the moderate to severe range.

While pain ratings of COT patients were typically unfavorable, about two-thirds of COT patients in both settings reported that they found opioids very or extremely helpful for their pain. These ratings did not differ between intervention and control clinics.

We assessed prescription opioid-use disorder using the prism interview, which assesses DSM-5 criteria. After dose reduction and risk stratification and monitoring had been implemented for more than 4 years, we observed no difference in the prevalence of prescription opioid-use disorder between COT patients from intervention and control clinics.

About 4 to 5 percent of COT patients reported moderate to severe prescription opioid-use disorder and over 20 percent reported problems, indicating at least mild prescription opioid-use disorder. These percentages are consistent with studies in other settings using DSM-5 criteria among COT patients.

We asked COT patients to rate their trust in their doctor's judgment in managing opioids. A large majority of patients in both settings agreed that they trusted their doctor's judgment in managing opioids. The trust ratings, however, were slightly lower in the intervention clinics than the control clinics.

We also asked COT patients whether they were worried that their doctor might discontinue their opioids. While most patients in both intervention and control clinics did not report that they were worried about their doctor discontinuing opioids, the percent that agreed that they were worried was somewhat lower in the intervention clinics.

In conclusion, what can we conclude about

these results? Regarding the dose-reduction initiative, we found that patients receiving lower opioid doses in the intervention clinics reported pain outcomes about the same as patients from control clinics who received, on average, much higher opioid doses.

Dose reduction may have lowered opioid overdose rates among COT patients, but our evaluation results for overdose were inconclusive, as I explained. The efforts to lower opioid doses into enhanced COT monitoring may have placed some stress on doctor-patient trust regarding opioid management. While patient trust ratings were typically high, they were slightly lower among patients in the intervention clinics.

Neither the dose-reduction nor the risk stratification and monitoring initiatives were associated with a reduced prevalence of prescription opioid-use disorder relative to controls. Prescription opioid-use disorder was equally common among COT patients in the intervention and control clinics. Thank you very

much for your attention.

DR. HERNANDEZ-DIAZ: Thank you very much.

We'll now continue with our last guest speaker today, Dr. Beth Darnall.

Guest Speaker Presentation - Beth Darnall

DR. DARNALL: Thank you very much. I'd like to thank the organizers for having me here today. I'll move quickly through a couple of these slides.

It's important to acknowledge the distinction between addiction and pain medicine and for content experts to provide advice within their scope of training. With that said, I'd like to declare that I have no addiction training, and I don't treat patients with addiction.

Up to 100 hundred million Americans are living with ongoing pain. This is to be distinguished from constant pain. This confers tremendous suffering to the individuals, as well as their families, and this has been discussed with some detail today.

On the topic of prescription opioid risks, I think we can agree there has been an uptick in

prescribing to the detriment of public health in recent years, and I'm specifically interested in the iatrogenic risks of opioids when they're taken exactly as prescribed. We have iatrogenic effects of prescribing, and now we have iatrogenic affects of de-prescribing. Of course, the question is how do we mitigate both of these?

This is of tremendous consequence now nationally, as up to 11 million Americans are taking daily opioids to manage their pain. A lot of my advocacy work is focused on protecting patient access to opioids when they are appropriate and necessary and protecting patients who choose to reduce their opioid dose.

Right now, there's a national focus on de-prescribing towards the goal of improving public health, but methods are being implemented that are neither patient-centered nor evidence-based, and we're seeing this nationally.

In 2016, the CDC put forward the opioid prescribing guidelines for chronic pain. These were not meant to be dose based, or to taper

patients to zero, or to set hard limits on prescribing. But what we're seeing nationally is that this is what's being implemented, that there has been broad misinterpretation of the CDC guidelines, so patients are being forced-tapered to zero or tapered to predefined doses. There's a failure to account for individual differences when de-prescribing, and a failure to monitor, protect, and to be flexible and meet the individual needs of the patient.

There has been a growing outcry against iatrogenic opioid-reduction risks and specifically to forced opioid tapering and also rapid tapering. This has been, really, something that has been a ground swell of interest and attention among clinicians, and patients, and advocacy groups alike, culminating with a focus on this with the FDA and also the CDC, to bring national prescribing into alignment with what has actually been put forward as best guidelines.

Dr. Sandbrink really set forward nicely some of the suicide data from the VA, and I'll look

forward to seeing those data published. What we're seeing nationally is that there's very little that's known about the risks of de-prescribing, among those being, foremost, suicidal ideation and also completed suicide. While this is not my area of expertise, I would just like to bring to attention that there is desperately needed better data on these iatrogenic risks that occur to patients in the course of de-prescribing.

Experts such as Dr. Kertesz and patients such as Anne Fuqua have been categorizing some of these data that have been collated from patient reports, family reports, and also social media, where patients have talked about being forced-tapered or cut off of their opioids, and that being the antecedent to a suicide completion.

Ultimately, we need better data on this topic, and we need systems and methods that protect patients. We need better data-capture systems. Tapering methods matter greatly. The health of the patient is paramount. Rigid dose-based policies violate the principles of patient centeredness and

expose patients to health risks. This is unsupported by both the CDC and the American Medical Association.

We've seen some data presented today that suggest that dose changes are associated with health risks. Patient-centered methods enhance patient engagement, and therefore their safety and their outcomes. Learning healthcare systems can facilitate research as well as point-of-care supports to characterize, screen, monitor, and provide safety measures to patients, clinicians, and healthcare organizations.

Multiple national agencies have put forward that there is an imperative to reduce opioid prescribing, and as well, multiple agencies and stakeholder groups have discussed the need to treat pain differently, to treat pain more comprehensively. This really is in alignment with what we know to be the bias psychosocial model of pain and also pain treatment. We've known for decades that pain is best treated when it's addressed comprehensively.

This is really at the core of what we call patient-centeredness. Pain is a biopsychosocial condition, and our treatments must reflect this fact. As well, our tapering protocols must reflect this fact. Patient-centerdness takes into account the whole person with pain along with their needs and their wants. We recognize that behavioral outcomes are optimized when patients willfully participate in their pain treatment programs.

How do we best help patients reduce opioid use when appropriate? Well, what we see is that tapering the wrong way is associated with an array of detrimental outcomes, harms, and often grave effects for these patients who are at very high risk for suicidal ideation or even suicide, so right methodology is key.

When you talk to patients about opioid reduction, their number one fear and concern is, unsurprisingly, increased pain. This is often born from personal experience, where patients who had been taking daily opioids maybe missed a dose or tried to taper themselves, reduce their own

medication, and experienced withdrawal symptoms, one of those being increased pain. Their personal experience has supported this very fact, that reducing opioids increases pain.

We see that when opioids are tapered the right way, the pain doesn't actually increase for patients, on average. These are VA data that were published in 2013. What's interesting is that, in this case, pain actually improves, and we see this across a multitude of studies. But here's the thing. These are typically inpatient or intensive programs that include a multitude of different providers. It's basically interdisciplinary pain care, so patients have these nice wraparound services and they get good outcomes for opioid reduction.

But these are programs that the majority of patients, the vast majority of Americans, will never access. They're costly, they're time intensive, and don't even try and get prior auth for these types of services. What we need are community-based solutions that are low cost, low

risks, and scalable, that effectively reduce health risks, they're structured, and they address this mutual anxiety among providers and patients alike when we're facing opioid reduction. Ultimately, we need to enhance patient willingness to try a gentle opioid wean.

This is work that myself and colleagues conducted within the past few years that was published in JAMA Internal Medicine last year, and this is community-based, patient-centered opioid tapering. This was conducted in Colorado clinics in the Denver area and also in rural areas, where patients were taking mostly high and very high-dose opioids.

There was a doctor who inherited these patients and cared for them, and we agreed to partner to conduct this study. We invited 110 patients in the clinic. Every single patient who was taking opioids, who was not actively receiving addiction treatment, was invited to participate in a patient-centered, opioid-reduction program that would see them work with their doctor to

participate in a gentle opioid wean over the course of 4 months, and then we would measure both their dose and their outcomes.

Patients were told that they had a high degree of control and how the taper was conducted. They could pause the taper if they wanted to. They could stop the taper if they wanted to. They could drop out of the taper if they wanted to. Nobody was forced to do anything in this study.

Of the 110 who were invited into this study, 82 of these patients agreed to participate, which was shockingly high. Of those 82, 68 actually enrolled in this study, and of those 68, 51 completed. That means that 17 patients did not complete. This is a 25 percent attrition rate, which is relatively low for this type of a study, particularly considering it's opioid reduction. There was only one patient characteristic that distinguished completers from those who dropped out. Those who dropped out of this study were higher on depressive symptoms.

We did not talk about opioid cessation with

these patients. We invited them to participate in reducing their opioids. Talking to patients about stopping their opioids can be terrifying, and stopping opioids isn't necessarily the point because we should never assume that any one patient should go to zero.

So we optimized patient choice and control for tapering. Again, participation was voluntary. They could control the pace. They could pause. They could drop out of this study. Tapering to zero was not the goal unless patients chose that goal. There were no predefined opioid ending doses, and patients partnered with their doctor to achieve their lowest comfortable dose over the 4-month study period.

Importantly, the taper was not unidirectional. This was a pragmatic study design, which means that we basically invited and enrolled everyone who wanted to participate. The only exclusionary criterion, as I mentioned, was active treatment for addiction.

These are the variables that we collected at

baseline, basic demographics, also morphine equivalent daily dose, pain, a few psychosocial measures, and then we followed them up, again, at 4 months. Along the way, they saw their physician about every 3 weeks for close follow-up.

These are the sample characteristics for the completers. As I mentioned, 51 completed the study. It's pretty typical of most of the data that has been presented throughout the day. Importantly, note that these patients had been on opioids for 6 years on average, with a range of 1 to 38 years. If you look at the morphine equivalent daily dose, it was close to 300. So this is a high-dose opioid sample, a range from 60 to over 1000 milligrams.

When you look at the final data at the end of 16 weeks, you see that opioid dose reduced precipitously. This was a success. We found that patients reduced their opioids on average by about half. We found that 4 patients reduced to zero on their own accord; 16 below 90 MEDD; and we found that depression did not worsen for these patients.

We also found that most of the other psychosocial characteristics did not improve with opioid reduction, but we weren't targeting them, so we weren't expecting this. When you just look at the dose decreased categories, you can see that patients were reducing their opioid doses by large amounts over the study period.

These are data plots, individual data plots for each person who was in this study. What you can see here in this graph, which is initial opioid dose, one of the questions we were asking was do patients on high-dose opioids successfully reduce their doses equally as those on lower doses? What we found was that the initial opioid dose did not predict taper response, meaning they were equally likely to have a favorable response to this reduction program.

Then we looked at pain scores, and we were interested in understanding if pain would worsen among our sample. In fact, we found that pain did not worsen. I do want to draw your attention to the fact that there are 3 patients who -- actually,

I'm sorry. There was 7 patients who had increased pain. They're over on the lower right-hand side, where some patients did have increased pain. And also the red dots on top, you see that some patients did increase their opioid doses over the course of this study.

Again, this was not a unidirectional reduction program, and I just highlight this so that we can be very mindful of the variability and the need to retain individual care within the context of this variability.

Now, what I presented to you before was percent change in opioid dose and no increases in pain. When you look at the data differently, when you look at it as an absolute decrease in opioid dose, we found that pain actually improved over the course of the study.

I've heard some people say that the key to successful opioid tapering is to just go very slowly, even in cases of forced opioid tapering, but our successful data do not support this conclusion. Rather, our pilot data show that our

patient-centered methods engaged patients in voluntary participation, and therefore, successful outcomes for patients who chose to partner with their healthcare clinician on a slow opioid taper.

Of course, it's not just about opioids or no opioids. We want to help people live better within the context of pain and engage more in activities that are meaningful to them. This necessarily involves behavioral interventions and pain education. This is really the topic and focus of the follow-on study to those prequel data that I just presented to you.

This is a study funded by the Patient-Centered Outcomes Research Institute, and the study name is EMPOWER, which is Effective Management of Pain and Opioid-Free Ways to Enhance Relief. We essentially took those patient-centered opioid tapering methods and applying them now in a national study. This is a comparative effectiveness trial of pain cognitive behavioral therapy and the Chronic Pain Self-Management Program conducted within the

context of patient-centered opioid reduction, and that's our study website if you are interested in understanding more details.

Patients who come into our study are agreeing to partner with the physician or healthcare clinician in a voluntary opioid-reduction program, so of course, everyone who comes in is taking daily opioid doses. Once they're enrolled and we collect their baseline data, they're randomized to one of three groups, which you can see there: CBT, chronic pain self-management program, or usual care, which is the taper only. This allows us to test the additive value of these behavioral interventions. We hypothesized that they will facilitate improved response to opioid and pain reduction.

We're studying this in almost 1400 patients taking long-term opioids for chronic pain in for western states. By the end of this year, we will be in 12 different clinics. We are using CHOIR as our learning healthcare system and also our informatics platform, and I will be discussing that

in just a moment. In terms of our eligibility criteria, basically, you can almost be taking any dose of daily opioids to enroll in EMPOWER. You have to have been taking opioids for 3 months and have pain for 6 months.

We had very minimal exclusionary criteria. The only thing that I really want to highlight is that we do exclude for moderate and severe opioid-use disorder. We do screen for opioid-use disorder and enroll patients with mild opioid-use disorder. We took great care in developing these screening protocols so that we could say with relative certainty that we are not inappropriately enrolling patients into EMPOWER who would require addiction medicine or other care pathways.

Our guiding principles for EMPOWER is that patient's safety and comfort is paramount. Patient-centeredness means we're integrating the patient's voice into the study design in the conduct of the study. Thirteen members of our research team have lived experience with chronic pain and several with opioid use.

Our preliminary work, patients told us that while they were willing to be randomized to a behavioral treatment group, they wanted to choose whether they tapered or not, and we listened to them. We recognize that the opioid tapering is not right for everyone, that there needs to be very careful patient selection, and also attention to the fact that some patients may need opioid therapy.

We monitor closely to identify and mitigate opioid tapering health risks, and we have systems in place, our learning healthcare system, to provide near real-time feedback to prescribing clinicians. We have flexible systems to attend to the patients' needs and wants.

Because our study is voluntary and patients can drop out at any time, the burden is on us to create a caring and safe system that allows patients to want to join and remain in EMPOWER. In our study, we train clinicians on our patient-centered methods. We train physicians and clinicians on patient-centered communication. We

help patients be heard and we create systems of support.

As I alluded to in the prequel study, we basically replicated our prior patient-centered tapering methods. I just want to highlight here that in the EMPOWER study, patients are partnering with their doctor to achieve their lowest comfortable dose over a full 12-month study period. Remember that in the prequel study, that only went to 5 months.

This is our learning healthcare system, CHOIR, which is the Collaborative Health Outcomes Information Registry, which we are applying throughout all of our EMPOWER study sites. This allows for granular data capture at point of care and also at each defined time point, so that we can do what is really lacking right now across the United States, both in regards to opioid prescribing and for de-prescribing; is that we don't know how patients are doing along the way. We only find out when there are big problems and it's too late.

What CHOIR does is it allows for this electronic data capture. You can see that the patient can complete these forms. They can tell us how they're doing, and these outputs are available both to the patient and to the provider, again, in real time.

For EMPOWER, we are assessing patients at baseline, 6 and 12 months. We're doing a comprehensive battery. We are assessing for opioid use and substance use. We assess the degree of choice that patients feel in their taper, et al., and also the readiness to taper. We're assessing taper beliefs, their satisfaction with the relationship with our clinician, and we allow for individual comments to be collated at every assessment. We deploy surveys weekly to patients while they're tapering. We assess for opioid withdrawal symptoms, mood, and also comments, and we deploy a broader battery at the monthly level.

This is a critical aspect of the EMPOWER study. This is close monitoring of patient response to opioid reduction. Alerts are sent to

providers in real time when patients endorse having withdrawal symptoms, or a decrease in mood, or stated differently, an increase in depressive symptoms or suicidality. We're taking this very seriously, monitoring very closely, and taking action as soon as possible, and we implement these supports over the course of the year-long study.

Importantly, patients who come into EMPOWER are getting better care than they would otherwise because we have these electronic monitoring and wraparound services. These are some of the outputs that just illustrate what's available to the providers, and you can see here this is a patient who's in EMPOWER. The orange dots showed the opioid decreasing over 6 months, while the blue Line is tracking their pain. Of course, there's a high degree of variability in pain, but what you can see is that over the course of 6 months, it's relatively static.

The providers can see how they're actually doing. Here, I'm just displaying baseline in 6 months, but you can see them at the monthly level

what's happening with their symptoms. Here, you can see that patients are doing better over the course of 6 months while opioids are being decreased.

This is a representative of a high-dose patient, where their opioids have reduced from 120 down to about 50 milligrams over the course of 6 months, while pain has remained relatively static. Here you can see, similarly, either improvements or patients remaining the same on some of these psychosocial outcomes.

Lastly, I would just like to say that we use peer-to-peer communication, so we have patients with lived experience with successful opioid reduction serving as communicators for patients who might be interested in tapering, or just need to learn more before they know whether they are willing to engage in tapering.

In conclusion, I would just like to say that, fundamentally, we need better data on the iatrogenic harms for opioid reduction. We need to apply better methods to support patients and

clinicians. We need learning health systems to provide close monitoring, and support and facilitate real-time alerts and action plans. Lastly, we must focus on patient protections as our highest guiding principle. Thank you very much.

Clarifying Questions

DR. HERNANDEZ-DIAZ: Thank you very much.

Are there any clarifying questions for the speakers? Again, we have plenty of time for discussion tomorrow, but clarifying questions for the presentation. If so, please remember to state your name for the record before you speak. And if you can, please direct your questions for a specific speaker.

Dr. Katzman? Dr. Marshall?

DR. MARSHALL: Yes. I had a question for Dr. Sandbrink. I just wanted to make sure I'm interpreting this correctly. If we could bring up slide 20, showing the overdose rates among veterans. The deaths due to natural and semisynthetic opioids seem to be fairly stable, and yet the prior data shows relatively significant

reductions in prescribed opioids in the VA populations.

I'm just trying to reconcile these two patterns. Would this suggest -- what would be causing -- you think that that black line might be decreasing if we're seeing reductions in opioid prescribing in the VA or their prescriptions coming from other sources, or what could be describing those patterns?

DR. SANDBRINK: Let me clarify the question. First of all, this is data for up to 2016, whereas in regard to the prescribing, I showed you data up to 2019, quarter 2, fiscal year 2019, knowing that our opioid reduction started in 2013 as a whole, our opioid safety initiative. The top line here, obviously as you pointed out, are the opioid overdoses. The one in regard to the prescribing natural and semisynthetic opioids, including methadone, that's a dark solid line.

This includes a prescription medication, but certainly this is not necessarily prescribed medication for that particular patient. This would

be also externally sourced or received any kind of opioid medication that falls into this category.

On the other hand, I think you can see that in the synthetic opioids, which is the Fenton [ph] derivatives, there is really this marked increase which started in 2013, very much in parallel with what the CDC shows for the nation, as well as the increase in heroin overdoses.

So what's the particular question and clarification request?

DR. MARSHALL: I guess the question is, then with that hypothesis, is the source of prescription opioids in these patients increasing from non VA sources? If the prescribed opiates from the VA are going down to maintain a flat overdose rate from those medications, are patients acquiring prescriptions from other sources, providers, or the street?

DR. SANDBRINK: That certainly is a possible explanation. I'm not sure that I can speculate in that regard. Maybe if we see the trend going out another year or two, it become more clear where

this is from. You are absolutely right, the reductions are certainly what we've seen in prescribing.

On the other hand, also our data shows that it's not necessarily all of the prescribing that in itself is the factor. Patients are at risk even at lower dosages. A patient who may have been taken down from a high-dose opioid therapy situation and on towards a more lower opioid dosage level could still die of an overdose from the prescription, especially if it's used in conjunction with other substances.

DR. HERNANDEZ-DIAZ: Dr. Becker?

DR. BECKER: Will Becker with a question for Dr. Darnall.

Congratulations on the EMPOWER study. It looks like really impressive work. We're funded for the other PCORI study that was funded in that round, and some of our approaches are very similar, so it's heartening to see that. I think we're kind of homing in on some core elements that are effective.

My question is, in terms of the scale-up of the program, could you just provide a little more detail about -- let's say a health system wanted to take up EMPOWER tomorrow, what would it mean in terms of resource outlay?

DR. DARNALL: Thank you for the question. We've had multiple organizations come to us right now, so what I'm going to tell you -- my response to you is in regard to what it would take to get the EMPOWER study embedded, not just EMPOWER methods, but the study.

In order to conduct the study, we need a full-time study coordinator on site, and that's really the bulk of the cost because we subsidize everything else at this point. If a site has a study coordinator available, we'd love to work with you and are happy to help get EMPOWER methods embedded into your system. The learning healthcare system is free, so we supply all of that at no cost.

Our patients are compensated for completing surveys. They're not compensated for doing the

taper. In fact, they have to pay their usual co-pays, et cetera. So we do supply compensation to patients for that, but it's nominal over the course of the study period.

We do have our two behavioral treatments embedded into each clinic. This is one piece that is important. Ideally, there is a psychologist, if not embedded in the clinic, somebody locally that we can train in the EMPOWER CBT so that they can deliver that behavioral treatment to EMPOWER patients who are assigned to that treatment group.

Our second behavioral treatment group is the Chronic Pain Self-Management Program, and that is often offered free of charge through municipalities such as through the aging council or in various cities. It would be on a case-by-case basis where I would work with people, but I definitely appreciate the question, and there is an open invitation to speak with anybody who might have interest in adopting the EMPOWER methods. And if you would like to study them, that's so the better. Thank you.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Zivin?

DR. ZIVIN: My question is for Dr. Von Korff. I was interested in hearing about your evaluation, but was also wondering if you could comment on the extent to which the intervention practices being different from the comparison practices because of their use of integrated care, and how that can potentially benefit the patients in other ways not explored here.

I understand that you showed slides where controlled practices did have higher morphine milligram equivalent doses, but I was wondering if you could comment on to what extent you thought the different types of practices affected your finding.

DR. VON KORFF: We controlled for the patient differences that we had automated data on, diagnostic data and demographic data that we control for. How different are community practices from integrated group practices, there's some difference.

I think it's a little bit hard to answer that question. Obviously, this is not a randomized

controlled trial. This is what happens in two systems under naturalistic conditions. I think the interesting thing from hearing the other two talks is I think there's starting to be convergence of results from randomized trials, say, of tapering. The couple that have been done are consistent with what Beth says. The outcomes are no worse and sometimes a little better, and doses are gotten down. Well, that's sort of what we found.

If I had to hang my head on science, I'd put it on a randomized trial. If you want to answer a question of overdose rates, you're not going to answer that with a trial because you need really large numbers. The overdose question I think is answerable now through naturalistic studies, the kind of study that we did, in a system like the VA or some of the Kaiser plans that have achieved larger dose reductions than we did a decade ago, relative to systems that are not as timely as in changing dose.

DR. ZIVIN: Thank you.

DR. HERNANDEZ-DIAZ: Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. A question for both Dr. Sandbrink and Dr. Von Korff. I'm interested in learning more, specifically, if you had support structures in place for those patients who are voluntarily tapering, both behavioral and emotional support structures. I know that they in both cases reported that doctors had dialogue with a single healthcare provider, but were there other programs in place for cognitive behavioral therapy, or pain management, or the emotional issues?

DR. VON KORFF: At that time, it was pretty meager. Even in behavioral health, this was 10 years ago, maybe we had one psychologist that was trained to manage pain. In general, mental health professionals don't know very much about pain.

MS. ROBOTTI: What about depression [inaudible - off mic].

DR. VON KORFF: Yes, depression, sure, they could get treatment for depression. But in the context of this intervention, there was not a comprehensive approach. You could refer to

physiatrists. We had very good physiatrists, and there was good access to that, and then there was an addiction specialist you could refer to, but it's not the sort of thing that anybody would cook up as a comprehensive approach to supporting patients being tapered.

The dose reduction was achieved on a population basis, part of it by holding the line on dose escalation, which I think is much easier to do than tapering. Tapering is tough, and a lot of the tapering wasn't full tapered. The percent of patients on opioids was no different between the two settings. It was done by partial tapers, and they often were not really large tapers.

MS. ROBOTTI: Thank you.

DR. SANDBRINK: Speaking for the VA, obviously, it's a large system. We have, as I pointed out, 6 million veterans under our care receiving care routinely from the VA. While we are implementing an opioid safety initiative, we are also system wide increasing access to non-pharmacological therapy and certainly

psychological therapy, access to CBT, but also acceptance and commitment therapy. Other mindfulness-based stress reductions and evidence is part of it, as well as chiropractic care and integrative health modalities.

That does not mean, though, that at every facility everything is available. I think we can tell you that when we look at all the VA medical centers in the United States, in continental USA -- I'm excluding Manila, which has a special situation and has low prescribing, but everybody has reduced opioid prescribing consistently since 2012.

Truly, everybody's following the same trajectory. On the other hand, I would be not honest if I didn't tell you that some sites have much greater access to pain psychologists that may be embedded in the pain clinic, whereas in other facilities, psychologists may be only available on a part-time basis, providing access to CBT.

So yes, I think the penetration is not there

where we would want it to be everywhere, but there is a general expectation that the services are available. But we also know that it's not consistently to the fullest degree everywhere.

DR. HERNANDEZ-DIAZ: Thank you.

DR. VON KORFF: Could I just add one thing?

DR. HERNANDEZ-DIAZ: Yes, clarifications, please.

DR. VON KORFF: In the current context of efforts to reduce inappropriate opioid prescribing, there are organized efforts to increase access to behavioral health kind of services for chronic pain patients by Kaiser. It's an important priority, so we're kind of where the VA is on that.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Urman?

DR. URMAN: Rich Urman. Just a quick question for Dr. Von Korff, slide 13; it's about chronic sedative use. I assume all these patients were also on opioids. Was the difference significant pre- and post-intervention, and were there specific interventions directed at reducing sedative use in these patients?

DR. VON KORFF: No, there wasn't. I'm trying to remember. There may have been mild advice to avoid sedative use, but it was not a major focus of the initiative. What I read is that it wasn't changing in Group Health, and it was going up a little bit in the control clinics.

DR. URMAN: Yes, that's what it looked like.

DR. VON KORFF: These results are consistent with a lot of research in other settings that find co-prescribing of sedatives, chronic use of sedatives. These are people who are getting at least 45 days supply in a 90-day period, so they're using sedatives on a regular basis. If you ask about any sedative use, it would be somewhat higher than this, so it's very common.

DR. URMAN: Right. Thank you.

DR. HERNANDEZ-DIAZ: Thank you.

Dr. Sprintz?

DR. SPRINTZ: Hi. Michael Sprintz. Dr. Sandbrink, I had two questions, actually. A quick first one is, are the benzos that are prescribed, are they prescribed by pain doctors, or

by psychiatry, and is there communication between the two?

DR. SANDBRINK: Benzodiazepines may be. Obviously, they're counting all prescriptions. That could be the primary care provider or the mental health provider. We do have mental health integrated into primary care. It's part of our emphasis in the VA system to provide patient aligned care teams that have access to mental health readily available.

Nowadays, in most situations, a primary care provider will be supported by a mental health provider in regard to benzodiazepine prescribing. I should point out that as we have an opioid safety initiative, we also have a psychotropic drug safety initiative, which, among others, includes an emphasis on evidence-based therapy for psychotropic medication, including benzodiazepines. We've had an interest in reducing the reliance on benzodiazepine prescribing in the system, in general, and not just in conjunction with opioid therapy, and truly get patients on long-term better

medications such as for PTSD.

DR. SPRINTZ: That's awesome. I had one other question. When you were doing opioid tapering, you mentioned that you were doing about 5 to 20 percent decrease every 4 weeks. Is there a reason why you didn't use buprenorphine for withdrawal management to enable either a faster taper, or are a lot of the docs' data in 2000 waivered? I'm talking about the physical dependence of opioid tapering, not necessarily saying they have an opioid-use disorder.

DR. SANDBRINK: Right. I think you absolutely right, that buprenorphine can be a wonderful tool, a very important tool, as you make adjustments to somebody's opioid prescription for pain. We certainly in the VA system support the use of buprenorphine for patients, where there is this concern about pain and opioid-use disorder or misuse of opioid medication, trying to improve safety.

As you know, one of the PCORI studies that Dr. Becker mentioned, among others, includes an arm

that has buprenorphine prescribing as an option for tapering. On the other hand, when we made our recommendations two or three years ago that we're pointing out, we did not have readily buprenorphine available to be prescribed off label for pain to the degree as we do nowadays. Even nowadays, it is a challenge.

So we're greatly interested in expanding access to us. We have our own initiative, the Stepped-Care Opioid Use Disorder training program to integrate access to medication-assisted treatment in general, including buprenorphine, in primary care settings, pain clinics, as well as mental health clinics, in addition to, obviously, our SUD programs.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Nelson?

DR. NELSON: Thanks. This is for Dr. Sandbrink as well. The work you're doing is great at the VA. I was struck, like Dr. Marshall was, with the disconnect between slides 16 and 20, in terms of a lack of a fall in essentially prescription opioid deaths, but a dramatic fall in

prescribing.

I guess what I was wondering, my explanation, or maybe what I wanted to see what you thought about, is the idea that the data in slide 16 that shows a reduction in prescribing overall might be masking, in a way, the fact we're prescribing less to subgroups of patients who are at lesser risk of overdose, but we're selectively not reducing the opioid prescribing to people or groups of patients who are at continued risk of opioid overdose.

Does that make sense? Is there a way to tell from the data, other than the general trend, if there are risk factors that we have or have not been able to identify in patients who continue to get opioids, and that's why the death rate in those patients is not falling?

DR. SANDBRINK: Obviously, if a provider is seeking to discontinue opioid medication, or it may be easier in patients, or maybe the low-hanging fruit, in regard to patients who are actually on low-dose opioid prescribing, you take them off and

you get them off and get them motivated.

I think part of what is hidden in the data is that these patients may reduce their dosages over a long time. So still, in the data on slide 16, they will be still counted as being on opioid medication, so they are not captured. If somebody goes from 400 to 300 to 200 to 100 to 50, and maybe now is on Percocet, a few tablets a day, they still will be counted in this system as being on opioid therapy and being on long-term opioid therapy. The only difference where you see it is in the high dosage.

So these patients may be coming down on low dosage, but they're still counted in the top graph, and they're going to still be counted in the center graph. All that I'm saying, this is just a summary data of all those patients, and many that are discontinued may potentially not be the highest dosage ones; rather, it's the lower dosage ones where you have a discontinuation.

I think we need to separate this from the gradual reduction that happens in regard to

tapering. I think cessation, discontinuing of somebody's long-term opioid therapy is very challenging, and it's particularly challenging in the high-dose opioid patients.

DR. HERNANDEZ-DIAZ: Thank you. Mr. O'Brien?

MR. O'BRIEN: Yes, thank you. For Dr. Darnall, compliments on your presentation and your program. Going back to slide 25, with the patients that were in the first 16-week program and showing a reduction down to 150, did those patients continue, and was there further reduction after that?

DR DARNALL: Great question, and this is a question I get asked a lot. This study was conducted largely in 2016 into 2017. Some of them who enrolled were actually in late 2015. We have conducted a follow-on study, and that's in progress. We have recent data for 25 of those patients.

So to answer your question, the short answer is no. We don't have data 8 months, a year out,

but what we are collating is the available data for these patients 3 years out, 2 and 3 years out at this stage. Those should be available later this summer. It's the million dollar question that people are asking us.

MR. O'BRIEN: In relation to that, with your second part, with your EMPOWER program, for the 1365 patients, are you seeing similar reductions for that group? I didn't see that in there.

DR. DARNALL: Yes. That study is active. We started enrolling last fall. We have 120 patients enrolled now across our multiple study sites. I presented two patient graphs towards the end. Those were for baseline 6 months. We don't have any 12-month data. Those were just two select graphs for 6 months, and we haven't analyzed any of those data as yet. I can tell you, just based on what we're hearing from patients -- we stay in very close communication with them, and we see the surveys come in, and we see their satisfaction -- patients are doing well.

MR. O'BRIEN: Well, it appeared in those two

graphs that the MME was going down about the same rate as the first study, the 6.8 [indiscernible] --

DR. DARNALL: Correct.

MR. O'BRIEN: -- with it. That's why I asked the question, if you had a total.

Last question, for the whole group, has there been any suicides or overdoses?

DR. DARNALL: No, none, not in the first study, although I recognize we only went to 4 months. So possibly, that could have been a tragic outcome afterwards and we may didn't catch that. I will say that I think the likelihood is low simply because it was voluntary. I think it's incredibly important to recognize that we had that 25 percent attrition rate, and that the distinguishing characteristic in those who dropped out was that they were higher on depressive symptoms.

My personal belief as a clinician is that part of patients fear, their absolute terror, is that they probably know that this is not a good

thing for them; that they need extra support. So because our study is voluntary, I believe that we have the opportunity to mitigate those tragic outcomes because we're not forcing them into territory that they're ill equipped to handle physiologically and emotionally.

MR. O'BRIEN: Thank you.

DR. JOWZA: Hi. Maryam Jowza. My question is for Dr Sandbrink. I wanted to clarify, with the taper that the VA
system initiated, was that voluntary or not?

DR. SANDBRINK: I think what I'm describing is a reduction that happens in our system. I think the one study that I showed by Travis Lovejoy and his group was that the largest, or the largest percent, about 85 percent, were actually provider initiated.

This is a subgroup that they looked at, but it's a representative sample that they pulled from all patients who had opioid dosage reduction.

In that regard, I can tell you that we believe that in our system, the largest number of

reductions that happened were actually provider initiated. But I think provider initiated is a very large group. This is a provider who maybe discusses with a patient, takes him to the side and says, "Hey, let's talk about your opiate medication," very much what we intend them to do. "Let's assess your risk, and let's talk about where do you want to be down the road."

The large majority of patients, and this is anecdotal from me seeing patients in the pain clinic -- most of our patients who come to us on opioid medication, or many of them, say "yes, down the road, years down the road, I really don't want to be on this medication anymore." They come to us as a 50 or 60 year old, and you ask them, "Where do you want to be in 10-20 years?" And they say, "Long term, I'd really like to get away from that." But often when you ask them, "What about today? Should we make a reduction?" usually they step back and say, "No, no, no. Let's not do it so soon."

DR. JOWZA: Thanks. Can I just ask a follow-up to that? Does your data, is it able to

capture an patients who left the VA system for their care?

DR. SANDBRINK: No. The limitation certainly is there in that regard. The patients who have been reduced, when I show the data -- this is prescribing from our VA pharmacies. If they get the medication from outside and it's not paid for by the VA system, if they go externally, no, that's not captured. That is certainly a possibility. We know it of some patients.

We do have a large community care program now that went really live just last week on June 6tn, our community care program. The goal is that community care providers who prescribe for the VA system, if we send the patient outside or if they go outside with the VA as an insurance system, they're supposed to submit the prescription to the VA's system for any prescription that's longer than 14 days. On the other hand, if patients have outside insurance as self-pay and seeing patients outside, that's not captured.

DR. HERNANDEZ-DIAZ: Thank you. Last

question, Dr. Mackey.

DR. MACKEY: First, well done to all three speakers. The clarifying question is to Dr. Von Korff. First of all, I really admire your elegant analyses. It's a two-parter.

You define your use case for this as people who are on 60-plus days over a 90-day period of time, and granted, it's in primary care. Did you account for people who had major surgeries in this?

For instance, total knees, total hips, thoracotomies can have a median time to opioid cessation into 30 to 45 days, meaning a decent number of these people, major surgeries, significant traumas, are still going to be on opioids and could meet your use case if the primary care doctors were prescribing instead of the surgeons.

DR. VON KORFF: Without getting into the weeds on how the evaluation was done, the definition of chronic opioid therapy that we used was what the system used to define chronic opioid therapy for purposes of implementing their

initiative. So when they produce statistics on their panel, on a physician's panel, they use that definition. We use the same definition.

DR. MACKEY: I get it. It was what it was.

DR. VON KORFF: And then the evaluation is organized quarter by quarter, so -- don't ask.

DR. MACKEY: The second part of that is, and it sounds like, was there any opportunity to stratify, then, your results, based on the duration of time that people were on chronic opioid therapy, with a hypothesis being that perhaps those who were on it for the shorter end of it may have been more likely to come down more easily or more rapidly than those, for instance, 10 years or however?

DR. VON KORFF: That would have been possible to do that. We didn't do that. In the survey, we only surveyed people that met our definition for three quarters in the previous year, but in the overdose analysis and other longitudinal analyses that we did, it was an open cohort.

Adjournment

DR. HERNANDEZ-DIAZ: Thank you.

The meeting for today is now adjourned. Sorry for the extra time. I can blame it on the great presentations, so thank you all very much.

Panel members, please remember that there should be no discussion of limiting topic among yourselves or with any member of the audience. We kindly ask all the attendees to dispose of any trash or recycling in the proper receptacles in the hallway and not to leave any waste items on the floor or tables, please.

Panel members, please remember to take all your personal belongings with you, as the room is cleared at the end of the meeting. Please leave your name badge on the table so that we can use it tomorrow. All other meeting materials left on the table will be disposed off. We will now adjourn the meeting for today, and we will be reconvening tomorrow morning at 8:30. Thank you.

(Whereupon, at 5:23 p.m., the meeting was adjourned.)