*FDA Public Virtual Scientific Workshop - Day 1*
*Morphine Milligram Equivalents*

---

*June 7, 2021*

---

*A Matter of Record*
*(301) 890-4188*

Page 1

FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research (CDER)

Public Virtual Scientific Workshop

Morphine Milligram Equivalents
Current Applications and Knowledge Gaps,
Research Opportunities, and Future Directions

Day 1

Monday, June 7, 2021
9:00 a.m. to 4:21 p.m.

Page 2

Meeting Roster

Shanna Babalonis, PhD
Assistant Professor
Center on Drug and Alcohol Research
College of Medicine, University of Kentucky

Jeffrey J. Bettinger, PharmD
Clinical Pharmacist Specialist, Pain Management
Saratoga Hospital Medical Group

Patrizia Cavazzoni, MD
Director - Center for Drug Evaluation and Research
FDA

Grace Chai, PharmD
Associate Director for Special Initiatives
Office of Surveillance and Epidemiology (OSE)
CDER, FDA

Brooke Chidgey, MD
Division Chief of Pain Management
University of North Carolina, Chapel Hill

Page 3

Sandra Comer, PhD
Professor of Neurobiology
Department of Psychiatry at Columbia University
Research Scientist VI
New York State Psychiatric Institute

Penney Cowan
Founder, CEO American Chronic Pain Association

Francesca Cunningham, PharmD
Department of Veterans Affairs

Nabarun Dasgupta, MPH, PhD
University of North Carolina at Chapel Hill
Departmental Affiliation
Gillings School of Global Public Health and
Injury Prevention Research Center

Thomas Emmendorfer, PharmD
Department of Veterans Affairs

Page 4

Perry G. Fine, MD
Professor of Anesthesiology
University of Utah
Salt Lake City

Jeffrey Fudin, PharmD, FCCP, FASHP, FFSMB
Albany College of Pharmacy and Health Sciences
Albany NY
Western New England University College of Pharmacy
Springfield MA
Stratton VA Medical Center
Albany NY
Remitigate Therapeutics
Delmar NY

David J. McCann, PhD
Associate Director of the Division of
Therapeutics and Medical Consequences
National Institute on Drug Abuse (NIDA)
NIDA, National Institutes of Health (NIH)

Mary Lynn McPherson, PharmD, MA, MDE, BCPS
Professor and Executive Director
Advanced Post-Graduate Education in Palliative Care
Executive Program Director
Online Master of Science and Graduate Certificate
Program in Palliative Care
Department of Pharmacy Practice and Science
University of Maryland School of Pharmacy

R. Daniel Mellon, PhD
Division of Pharmacology/Toxicology for
Neuroscience
Office of Neuroscience (ON)
Office of New Drugs (OND)
CDER, FDA

Tamra Meyer, PhD MPH
Team Lead, Nonmedical Use Team #1
Division of Epidemiology II
OSE, CDER, FDA



Maria Luisa Molinari, MD
Senior Clinical Assessor at the Medicine and
Healthcare Products Regulatory Agency (MHRA)
PGDip in Drug Development Science
King’s College London

Jennifer Nadel, MD
Medical Officer
Division of Anesthesiology, Addiction Medicine, and
Pain Medicine
ON, OND
CDER, FDA

Mary Therese O’Donnell MD, MPH
Medical Reviewer
Division of Anesthesiology, Addiction Medicine and
Pain Medicine
ON, OND, CDER, FDA

Justin Pittaway-Hay, PhD
Medicine and Healthcare Products
Regulatory Agency (MHRA)



Chad J. Reissig, PhD
Behavioral Pharmacologist
Controlled Substance Staff
Office of the Center Director (OCD)
CDER, FDA

Friedhelm Sandbrink, MD
National Program Director for Pain Management,
Opioid Safety and PDMP (PMOP)
Specialty Care Services
Veterans Health Administration
Director Pain Management
Department of Neurology
Washington DC VA Medical Center

Judy A. Staffa, PhD, RPh
Associate Director for Public Health Initiatives
OSE, CDER, FDA



Donna A. Volpe, PhD
Division of Applied Regulatory Science
Office of Clinical Pharmacology (OCP)
CDER, FDA

David A. White, PhD
Director of National Institute on Drug Abuse’s
Addiction Treatment Discovery Program
Division of Therapeutics and Medical Consequences
NIDA, NIH

Corinne Woods, RPh, MPH
Team Lead, Drug Utilization Team
OSE, CDER, FDA

Kun Zhang, PhD
Health Scientist
Division of Overdose Prevention
National Center for Injury Prevention and Control
Centers for Disease Control and Prevention (CDC)

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)





P R O C E E D I N G S

(9:00 a.m.)

Welcome and Panelists Introductions

DR. CHAI: Good morning and welcome. Thank you for joining us virtually for this Public. Scientific Workshop on Morphine Milligram Equivalents: Current Applications and Knowledge Gaps, Research Opportunities, and Future Directions. I would first like to remind everyone to please mute your line when you are not speaking.

My name is Grace Chai, and I am the associate director for Special Initiatives in the Office of Surveillance and Epidemiology under the Center of Drug Evaluation and Research here at FDA, and I will be chairing this meeting.

First, I would like to start with a few housekeeping details. Meeting materials, including the agenda, list of speakers, and panelists' names and the disclosures, are available online, posted on the meeting website.

Please note, the meeting recording and slides are expected to post at a later date,

Page 13

approximately two to three weeks. Transcripts will be posted at a later date, closer to August. The public docket as cited in the Federal Register notice will be open through August 9, 2021 for your feedback. You are encouraged to post further comments there.

Today, the first break will occur around 11 a.m., and lunch is scheduled for approximately 12:25 p.m. today. Please plan accordingly.

We will now begin with introductions of our meeting participants in alphabetical order. When I call your name, please introduce yourself by stating your name and affiliation, and please remember to unmute your line before you speak and to mute once you have finished.

Dr. Shanna Babalonis, could you introduce yourself, please?

DR. BABALONIS: Sure thing. My name is Shanna Babalonis, and I'm an assistant professor in the Center on Drug and Alcohol Research and the College of Medicine at the University of Kentucky.

DR. CHAI: Thank you.

Page 14

Dr. Bettinger?

DR. BETTINGER: Hi, everyone. I'm Dr. Jeff Bettinger. I'm a pain management clinical pharmacist working with Saratoga Hospital Medical Group in Saratoga, New York. I'm very excited to be here today. Thank you.

DR. CHAI: Thank you.

Dr. Chidgey?

DR. CHIDGEY: Hi. My name is Brooke Chidgey. I'm the division chief of pain medicine at UNC in Chapel Hill, and the medical director of our pain clinic there.

DR. CHAI: Thank you.

Dr. Comer?

(No response.)

DR. CHAI: Dr. Comer, can you hear me? Are you connected with audio?

(No response.)

DR. CHAI: We'll come back to Dr. Comer.

Ms. Penney Cowan?

MS. COWAN: Good morning. My name is Penney Cowan, and I'm founder and CEO of the American

Page 15

Chronic Pain Association.

DR. CHAI: Thank you.

Dr. Cunningham?

DR. CUNNINGHAM: Good morning. My name is Fran Cunningham. I'm from the Department of Veterans Affairs. I'm the director for the Center for Medication Safety and associate chief consultant, PBM.

DR. CHAI: Dr. Dasgupta?

(No response.)

DR. CHAI: Dr. Dasgupta, can you hear me? We weren't able to hear you.

(No response.)

DR. CHAI: We'll come back.

Dr. Emmendorfer?

(No response.)

DR. CHAI: Dr. Fine?

(No response.)

DR. CHAI: Dr. Fudin?

DR. FUDIN: Hello?

DR. CHAI: Oh, hi. Could you introduce --

DR. FUDIN: This is Dr. Fudin.

Page 16

DR. CHAI: Thank you.

DR. FUDIN: Hi. Dr. Fudin from Upstate New York. I'm affiliated with the Stratton VA Medical Center and also founder and president of Remitigate Therapeutics, and have affiliations with both Albany College of Pharmacy and Western New England University College of Pharmacy. My specialty is pain management.

DR. CHAI: Thank you, Dr. Fudin.

Dr. McCann?

(No response.)

DR. CHAI: Please remember to unmute your lines. I'll come back to the names we've missed.

Dr. McPherson?

DR. McPHERSON: Good morning. This is Lynn McPherson. I'm a professor at the University of Maryland School of Pharmacy in Baltimore and executive director of Advanced Post-Graduate Education in Palliative Care.

DR. CHAI: Thank you.

Dr. Molinari?

DR. MOLINARI: Hello, everybody. I'm Maria

Page 17

Molinari. I'm a clinical medical assessor from the MHRA in the UK.
DR. CHAI: Thank you.
Dr. Pittaway-Hay?
DR. PITTAWAY-HAY: Hello. It's Justin Pittaway-Hay. I'm a PK assessor at the MHRA.
DR. CHAI: Thank you.
Dr. Sandbrink?
DR. SANDBRINK: Good morning. I'm the national program director for pain management, opioid safety, and prescription drug monitoring programs in the Veterans Health Administration. I'm the director for pain management at the Washington, D.C. VA Medical Center, and I have academic affiliation with the Uniformed Services University in Bethesda and George Washington University in Washington D.C.
DR. CHAI: Thank you.
Dr. White?
DR. WHITE: Good morning. My name is David White. I am the director of the Addiction Treatment Discovery Program at NIDA, which is part

Page 18

of NIDA's drug development program, overseen by the Division of Therapeutics and Medical Consequences.
DR. CHAI: Wonderful. Thank you.
And Dr. Zhang?
DR. ZHANG: Good morning. My name is Kun Zhang. I'm a health scientist with the Division of Overdose Prevention at CDC.
DR. CHAI: We'll try one more time.
Dr. Comer, can you see if you can unmute your line and introduce yourself?
DR. COMER: Can you hear me now?
DR. CHAI: Yes. Thank you.
DR. COMER: Hi. I'm Sandy Comer. I'm a professor of neurobiology at Columbia University in the Department of Psychiatry, and I'm the director of the opioid laboratory there.
DR. CHAI: Thank you, Dr. Comer.
Dr. Dasgupta, are you able to unmute your line and introduce yourself?
(No response.)
DR. CHAI: We'll work with you on that.
Dr. Emmendorfer, are you able to unmute your

Page 19

line and introduce yourself?
(No response.)
DR. CHAI: And Dr. Fine, are you able to unmute your line and join us, or introduce yourself?
(No response.)
DR. CHAI: Okay. We'll work on your connection today.
We also have another representative from MHRA UK joining us. We're very fortunate to have Dr. Parkinson joining us for the next two days to help with clarifying questions as well as panel discussions.
Dr. Parkinson, could you introduce yourself, your affiliation, and state your disclosures?
DR. PARKINSON: Hello. I'm Nicola Parkinson. I'm a scientific assessor at the MHRA. Yes, I've been leading on the opioids review here in the MHRA, so I'll be looking forward to hearing from you all. Thank you. I hope you heard me ok.
DR. CHAI: Yes. Thank you. That was great.
Next, I will introduce our FDA speakers,

Page 20

moderators, and panelists. Again, my name is Grace Chai, and I'm the associate director for Special Initiatives in OSE under CDER.
Dr. Mellon, could you introduce yourself?
DR. MELLON: Good morning. My name is Dan Mellon. I am a deputy director of the Division of Pharmacology and Toxicology for Neuroscience in the Office of New Drugs, Center for Drug Evaluation and Research, FDA.
DR. CHAI: Dr. Meyer?
DR. MEYER: Good morning. My name is Tamra Meyer. I'm an epidemiologist and team lead for the Nonmedical Use Team Number 1, in the Office of Surveillance and Epidemiology in CDER.
DR. CHAI: Dr. Nadel? Jennifer Nadel?
(No response.)
DR. CHAI: We'll come back.
Dr. O'Donnell?
DR. O'DONNELL: Good morning. My name is Mary Therese O'Donnell, and I'm a medical officer in the Division of Anesthesiology, Addiction Medicine, and Pain Medicine in the Center for Drug

Page 21

Evaluation and Research at the FDA.
DR. CHAI: Thank you.
Dr. Reissig?
DR. REISSIG: Good morning. My name is Chad Reissig, and I'm a pharmacologist with the controlled substance staff at FDA.
DR. CHAI: Thank you.
Dr. Staffa?
DR. STAFFA: Good morning. I'm Judy Staffa. I'm the associate director for Public Health Initiatives in the Office of Surveillance and Epidemiology in CDER at FDA.
DR. CHAI: Thank you.
Dr. Volpe?
DR. VOLPE: Good morning. My name is Donna Volpe. I'm a researcher in the Division of Applied Regulatory Science in CDER, in the FDA.
DR. CHAI: Corinne Woods?
MS. WOODS: Good morning. My name is Corinne Woods. I'm one of the team leads on the Drug Utilization Team in the Office of Surveillance and Epidemiology at CDER, at FDA.

Page 22

DR. CHAI: I'll try one more time.
Dr. Jennifer Nadel?
DR. NADEL: Hi. This is Jennifer Nadel. I'm a medical officer in the Division of Anesthesia, Analgesia, and Addiction Medicine.
DR. CHAI: Thank you.
Thank you to everyone for being here. We know that this is a busy time, so we appreciate the time you're taking out for the next two days.
Our goal is that this meeting will be a fair and open forum for discussion of these issues that we're about to discuss and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals are asked to mute and unmute to speak only when recognized by me or other moderators to help facilitate this virtual meeting.
During this meeting, only panel members consisting of all invited speakers and panelists will be able to ask clarifying questions of the presenters and participate in the panel discussions tomorrow.

Page 23

We have scheduled clarifying question sessions following groups of presentations. We encourage all panelists to jot down any clarifying questions you may have for presenters. Please take note of the times for clarifying question sessions on the agenda.
Due to scheduling conflicts, a few participants will not be able to join us tomorrow on day 2. We ask for any clarifying questions for Dr. Emmendorfer, Dr. Cunningham, Dr. Fudin, Dr. Molinari, and Dr. Pittaway-Hay to be asked today for their presentations. We look forward to a productive meeting.
To kick off this two-day scientific workshop, we will now hear opening remarks from Dr. Patrizia Cavazzoni, director of the Center for Drug Evaluation and Research at the U.S. Food and Drug Administration.
Thank you, Dr. Cavazzoni.
(No response.)
DR. CHAI: Are you able to unmute your line?
DR. CAVAZZONI: Yes, I am. Can you hear me ok?
DR. CHAI: Yes. Thank you.
DR. CAVAZZONI: Very good. Very good.
Opening Remarks – Patrizia Cavazzoni
DR. CAVAZZONI: Good morning, everyone, and welcome to our public workshop. It is an honor to be with you today. A special thank you to the attendees and organizers of this workshop for coming together, especially in light of the extraordinary challenges and hardships we have all faced this past year.
Indeed, this is a critical time in our nation's history. As the COVID-19 pandemic progressed, we saw drug overdose deaths reach a record high, and the opioid crisis continue to devastate families and communities across the Nation.
Throughout it all, the opioid crisis has remained an urgent public health priority for the FDA. Using all available evidence and tools at our disposal, the agency is committed to reversing this trend and ensure safe prescribing of all

Page 25

medications with the potential for abuse.
We at FDA recognize that the increased isolation of the past year may be a contributing factor in the rise in the number of overdose deaths over this period, a complication of the documented psychological distress caused by the imposed isolation during the COVID-19 pandemic.
This past year has been tough for everyone, but in particular for patients. As part of FDA's efforts to address the opioid crisis, we acknowledge that this is an ongoing effort to strike the right balance between providing access to pain medication for those who need them, as well as managing the variety of risks posed by these drugs.
Employing evidence-based strategies to responsibly utilize analgesics will be more important than ever to ensure that patients stay safe while being treated for pain, which often requires complex and multimodal pain management.
Opioid conversion factors such as morphine milligram equivalents, or MMEs, are one tool

Page 26

research, clinicians, and policymakers have used to study the use and risks of opioids and to try to reduce those risks.
With this workshop, we intend to focus on the science. First, describing the scientific basis for MMEs along with gaps, challenges, and difficulties in using them; and second, identifying the evidence in science that may still be needed to ensure their appropriate use for safe opioid prescribing.
A stronger understanding of complex dose-response relationships across opioids, as well as patient factors that may influence the probability of experiencing adverse events, are needed to better utilize MMEs as a clinical tool to help ensure appropriate opioid dosing and reduce the risk of opioid overdose without sacrificing adequate pain control in patients for whom it can be safely achieved.
MMEs have a role in informing the safe and judicious prescribing of opioids. A more nuanced evidence-based understanding of the complexities

Page 27

embedded within MME conversion factors can help us refine our knowledge and guide the safe and effective use of opioids.
As an agency, we are highly conscious of individualized patient care and acknowledge that simple answers are desirable but not always realistic.
Although we recognize that the discussions held at this meeting may ultimately have implications for policy or regulatory applications of MMEs, these areas will not be the focus of today's meeting.
With this meeting, we are seeking to build upon the science, including from our previously held 2013 "Opioid Conversion" workshop. We are seeking to encourage scientific discussion and work to enhance our collective understanding and evidence and equip clinicians and other stakeholders with the information they need to ensure the best patient care and public health outcomes.
It is clear that the science on this topic

Page 28

has evolved over the years, and this is a great opportunity to reflect on the current state of knowledge for this important issue. We encourage all stakeholders, including federal partners, our colleagues in academia, and fellow researchers, to join us in advancing our understanding in this space.
Realizing that we cannot accomplish this alone, FDA looks forward to continuing to work with you to make a positive impact on the trajectory of the opioid crisis.
With that, I'd like to thank you all for coming and being part of this thoughtful discussion.
Presentation – Grace Chai
DR. CHAI: Thank you, Dr. Cavazzoni, for your opening remarks. It's really helping to set the stage for these next two days.
I'd like to move on to my introduction presentation to help clarify what the goals of this meeting are. I would also like to express my thanks and appreciation to all the presenters and

Page 29

panelists for their time and efforts in preparation for this meeting, and would especially like to acknowledge and thank all those that have devoted months of hard work to prepare for this two-day virtual scientific workshop to inform an advance on the science underlying morphine milligram equivalents or MMEs.

First, I'd like to start with what is an MME. Here's one definition, courtesy of our CDC colleagues. MME is defined as the amount of milligrams of morphine an opioid dose is equal to when prescribed. Calculating MME accounts for differences in opioid drug type and strength and has been used for years in patient care, such as to inform on starting dose when converting from one opioid to another.

More recently, MMEs or other similar terms are increasingly being used to indicate abuse and overdose potential and to set thresholds for prescribing and dispensing of opioid analgesics.

To set the stage for this two-day workshop, here are the purpose and goals of the scientific

Page 30

meeting. The purpose of this meeting is to bring experts and stakeholders together to discuss the scientific basis underlying morphine milligram equivalents, which are widely used as metrics in multiple areas throughout the healthcare system.

Speakers over the next two days will present on a range of topics regarding the science underlying the space which we are referring to as MMEs. Presentations include a discussion of the uncertainties and complexities, not only in the MME conversion factors themselves but in the calculation and application of MMEs, as well as the use of MMEs as risk predictors for overdose, non-medical use, or the development of opioid-use disorder.

Tomorrow afternoon will be devoted to panel discussions when our speakers and additional panelists will discuss key topics on the state of the science and inform on a future research agenda. This workshop is to highlight the science and encourage all stakeholders, including government agencies, academia, and others, to join in

Page 31

contributing to advancing the science in this space.

Ultimately, patients and public health continue to be our priority. We will start the day by hearing how science impacts patients, reinforcing the need for a better understanding and advancement of the science in this space.

Today, we will hear the patient's perspective both from an invited speaker, as well as during the public comment session. To help facilitate a productive meeting to meet these goals, I would also like to clarify what we will not focus on in this two-day meeting.

We recognize that the workshop's discussion of the science may have implications on specific applications of MMEs, however, discussion of specific regulatory actions, policies, and applications of MMEs is not the focus. Our goals are for a better collective understanding and future collaborative advancement of the science underlying MMEs.

Presentations today will provide more depth

Page 32

into these topics, including the history and scientific basis of MMEs, both what is known as well as gaps in the science, as well as the varying uses of MMEs across different applications. Presentations will also show the existence of multiple resources, including reference tables, guidelines, online calculators, and other tools that may use or cite different MME factors. Presentations will also highlight the challenges regarding individual patient and drug characteristics that may influence the use and calculation of MMEs.

Recent public health focus includes the use of MMEs as a measure of dose often in tools to address the opioid crisis. Some of this interest in MMEs may have come from epidemiologic studies showing a convincing association between increasing daily dose of opioid analgesics and increasing risk of overdose. These studies generally used daily MME thresholds of 50 or 90 MMEs to assess risk. Studies have also examined the association between daily dose and adverse outcomes, but it's important

Page 33

to note that these studies are challenging to conduct and causality is unclear.

Given the complexity about MMEs and how they are used, I will take some time to walk through this influence diagram we created to help illustrate the complexity, as well as to structure some of the topics and discussions you'll see and hear over the next two days.

This is not a comprehensive model, nor was it designed to be. The variables represented here were drafted to give the system view of many moving parts that should not be considered in isolation. While we do not have complete information on many aspects of this diagram, the diagram shows the most common stakeholders that may use them and the potential resulting influences. The arrows demonstrate a believed relationship that is a possible influence of one factor on another that connects the uses to potential outcomes.

It all starts with the science, what is known, as well as emerging research, which inform the space of MMEs or opioid comparisons. MME

Page 34

factors are often used in various algorithms to calculate MME per day or other measures. In addition to varying patient and drug characteristics that influence the use of MMEs, the existence of multiple online calculators and tools, as well as variability and calculations amongst healthcare providers themselves, complicate these factors.

Many of our presenters will be going in depth into these topics. These areas in this blue box comprise the main focus of our scientific workshop over these two days, however, the application and use of MMEs is critical in the consideration of the science and how science informs the application of MMEs.

Uses of MMEs have expanded into varied uses across clinical practice in prescribing, and dispensing, as well as in reimbursement and regulation at various levels and in research, both in the U.S. and globally. In addition to our US-based experts and stakeholders, we are also fortunate to have our colleagues from the United

Page 35

Kingdom joining us today to provide insight from their perspective.

As stated earlier, our common priority is patients and public health and how science impacts patients, highlighting the importance of understanding the science. The opioid crisis is highly complex. This diagram illustrates some of the complexities, as well as the potential wide-ranging influences of MMEs.

As Dr. Cavazzoni spoke about, the opioid crisis continues to be a critical public health priority. We understand and recognize the need and desire to discuss much more than the goals we have outlined today. We also recognize discussions may have future implications on the application of MMEs. However, as stated earlier, we will not discuss changes to specific policies or seek to undermine specific uses of MMEs.

Enhancing evidence-based approaches by collectively leaning in to inform and develop the science where it is needed is what we are here to facilitate today, with the goals of better

Page 36

equipping all stakeholders with a more thorough understanding of the science underlying MMEs.

Over the next two days, you will hear from many experts and stakeholders in this field. Meeting materials are available online, including the agenda with the order of presentations, titles, and speakers. Tomorrow, we will hold the panel discussions. Please take note of the panel discussion questions to be discussed, also available online.

For your convenience and reference, here is the agenda for the next two days. I'd also like to orient you to the panel discussion questions that we will be discussing tomorrow for your reference, as well as to prepare you for tomorrow.

I'd like to thank you for your time and attention. Next, we will hear from Ms. Penney Cowan, founder and CEO of the American Chronic Pain Association, on a patient's perspective and how science impacts real-life experiences. Thank you.

Presentation – Penney Cowan

MS. COWAN: Thank you, and good morning,

Page 37

everyone. Again, my name is Penney Cowan. I'm the founder and CEO of the American Chronic Pain Association.

Before I start -- I'm going to talk about the impact of science on real-life experience -- just a little background into the American Chronic Pain Association. We've been around since 1980. We facilitate peer support groups and education for individuals with chronic pain and their families so that they can live more fully in spite of their pain, and to raise awareness among health care, policymakers, community, and the public at large about many issues of living with chronic pain.

I want to start with the time line of where I have seen pain go over the last 40 years since I've been involved. In the late '70s, one of the things that really stood out -- and I had my own personal experience with it -- was pain management programs, the interdisciplinary or multidisciplinary pain programs that really started with the movement by John Bonica. All of these

Page 38

programs were very interactive. They provided all of the necessary skills, and support, and medical interventions that a person needed to really begin that journey from patient to person.

So I was fortunate enough to spend time at the Cleveland Clinic at an inpatient program, which many of them were. As I graduated from the program, I realized that while they taught me how to live with my pain, they didn't take it away because there's always going to be some level of pain.

To give you a background on where we're at, our goal of pain management is to improve quality of life and increase function while reducing one's sense of suffering. That's truly important. Nowhere does it say get rid of the pain. So people teach you how to live with pain, how to manage it, but it's up to that individual to continue to maintain their wellness over a long period of time.

Thus, that's why I started the American Chronic Pain Association, for a variety of reasons. At one point as we got going, I would get an email

Page 39

from CARF, which is the Commission on the Accreditation of Rehabilitation Facilities, once a month giving me information about every CARF-accredited interdisciplinary/ multidisciplinary pain management program in the country. And there were close to 2,000 of these, both inpatient and outpatient.

Then in the late '80s, what I saw is a real shift in the way people were looking at managing pain. I think a lot of it had to do with the payers, because instead of reimbursing for the interdisciplinary/multidisciplinary pain management programs, they saw that the interventionalists, the TENS units, the intrathecal pumps, and the nerve blocks, were really just as effective and a lot more cost effective.

So we saw a real cut back in the number and availability of pain management programs. The more the interventionists came along and push and took over pain management, it was deemed to be the accepted way.

The whole time, from the time I entered,

Page 40

even through all the time with interventionists, one of the things that I kept hearing over and over again was that opioids were not the way to manage pain. Ed Covington was actually the director of the pain program when I went through it, and I can remember him saying, "If you take an opioid, a person with pain is going to have two problems. They're going to have pain and they're going to be addicted." So that sort of has stuck in my mind all this time.

Then in the late '90s, here come people saying, "Oh, opioids are ok to take," and it was probably the most confusing thing. And it was really hard for me to accept because for so long it was like that wasn't the thing to do. We had to look at all the other components of pain management in order to help people manage their pain, but all of a sudden opioids were the thing to do.

So here we are through the late '90s into the 2000s, and as we saw what happened, we had a huge influx of people taking opioids. We saw the media say -- and I can remember reading in the

Page 41

paper, "get the pills, crush them, snort them." It was an amazing thing to watch this grow throughout the country, to see the number of deaths. But it really had an impact on people living with pain as well.

So now what we're seeing back here in 2021 is that people are looking at what we had back in the '70s, which is the integrative pain management program and all of the other components that are available to people with pain, and it's kind of interesting.

One of the impacts of where people with pain are now struggling today was the release of the CDC guideline for chronic pain management. They were for primary care. They were intended for primary care clinicians, not for pain management physicians, and there's a huge difference there.

One of the things I found really interesting in talking to many people, both healthcare professionals -- no one, very few of the people I talked to, when they would tell me what they thought about them, I'd ask them, "Well, did you

Page 42

read them?" And it's, "No." They didn't read the whole thing. They took pieces from it, and that's exactly, I think, what a lot of the media did, and they reported.

So the interpretation was that we shouldn't prescribe; providers shouldn't be using opioids anymore. You'd see this in all the media, and unfortunately they have a huge amount of power on the opinion of the public. So we saw a lot of that happen.

So what happened? Providers became afraid to prescribe. And again, I would hear that some physicians, their offices were raided. They were taking all their medical records. They were a couple of them even put in jail. And I can totally understand. Why would they risk all of the effort, the energy, the money, the time to learn their practice only to have it taken away because they're prescribing opioids?

A lot of these were pain management providers, and if you think about it, they're the ones who were prescribing the opioids. They were

Page 43

the ones who were taking care of people with chronic pain.

I think at one point we have to step back and look at there are different groups of people who are using large doses of opioids. There are people who truly are people living with pain, and they're taking them only because they are able to now function and be a productive part of society. And when they were taken away, I know we got a lot of calls from people that I'm going to lose my job; I can't work. I mean, it was really sad; where there were other people that were using them recreationally and just using them for the wrong reason.

So there are different populations, and I think everybody got lumped into one thing. If you're taking an opioid, it was like that's the group you belong in. So many, many people suffered for a very long time, and many are still suffering.

One of the things that we wanted to do was find out what was the impact of our members, so we did a survey about a year later just to understand.

Page 44

We surveyed a little more than a thousand people, and some of the things that we found were that 56 percent had difficulty obtaining a prescription for their pain medication. These are people that had been taking it, functioning and working, and now 56 percent of them were having trouble.

Thirty-nine percent of the physicians no longer prescribed their medications. They just said I'm not prescribing. Again, it was that fear of repercussions because they were writing too many prescriptions.

Sixty-three percent of the pharmacies carried only a limited supply of the medication, and that's because a lot of them were being robbed. There were a lot of burglaries happening at pharmacies, so they just weren't carrying them anymore; because 28 percent of them said that they don't even carry that medication anymore, and they would put signs up.

I know a number of people, where they go to their healthcare professional, and they'd see signs in the window, "We don't prescribe opioids

Page 45

anymore." I mean, they put them right on their windows, right as you go into the office, into the door.

I think one of the saddest things that we saw in this survey is that 47 percent of the respondents have contemplated suicide because they cannot find relief from their pain, and that's I think really, really sad. And when it comes to actually going to the pharmacy, 7 percent -- and I found this really interesting -- were asked to produce their complete medical record.

I don't know about you, but I don't know anyone who carries around or even has access to their complete medical record to give to a pharmacist. Fifteen percent of them were simply refused to refill their prescription, and there was absolutely no reason given for why they're refusing.

One of the problems is 18 percent of the pharmacists were concerned over the prescription. And what happened there is they would actually call the prescriber, the healthcare professional, and

Page 46

question them as to why they were giving this person high dose, so many of them. And providers, again, they don't have time for all of those calls, and why would you have to justify? Why would they, the person who is treating this person with pain, who knows them, who have been treating them, have to answer to the pharmacists when those kinds of calls came in? So again, one of the reasons they just stopped prescribing, it just wasn't worth the grief.

So what did people do when they can't get their medications? They wanted and needed to live a normal life. And again, those are the calls we would get, people just wanting to get back to work, to be able to function, to provide for their family. But some of them just simply suffered. They suffered because they had to reduce it. Some hoarded their medications, taking a lot less than the amount that was prescribed for them so they wouldn't run out. They tried to space it over a long period of time.

Many of them would go to the emergency room

Page 47

seeking relief, and they were sort of the ones that were called frequent flyers, where they would be refused after a while. And there were a few people that were actually arrested right out of the ED. Others self-medicated with alcohol and marijuana, and some were so desperate enough to turn to the street drugs, and I think that's really where we saw a lot of the problem and a lot of the heartbreak.

Here are some of the quotes, and we had hundreds of these quotes in this survey. We always give people an opportunity to share their thoughts and feelings. These are quotes. I'm going to read them.

"I started using illegal opioids after I was unable to get my medication."

"I will have no choice but to commit suicide when I'm no longer able to travel out of state every three months to get my prescription."

"I have fraudulently called in prescriptions and bought them off the street. The amount of guilt I feel is extraordinary. I have ruined my

Page 48

life."

"I take meds to make me sleep as much as possible. I lie on the couch and watch TV and cry. I vomit a lot. And when I can't handle it anymore, I tell my wife to take me to the ER."

This is one thing that people don't realize; it's not just the person with pain that's suffering. Family members are also directly impacted by this crisis and the impact it's having on that person with pain, and their ability not to work, and their inability to manage the pain.

"I suffer in immense pain. This tears my family apart."

"I stay in bed in agony, weeping, depressed, can't eat, can't work, sleep, or function. No quality of life. I feel lost, scared, and alone. Pain takes over my whole body and all aspects of my life." Those are just but a few of the many quotes we got.

I want to step back and take a look at how did we get to this point. I think one of the interesting things is that we don't look at

Page 49

expectations. We don't look at the expectations of the person with pain or the healthcare professional. In other words, when a person goes to their healthcare provider, how often are they asked what's their goal of pain management? They're asked their symptoms, their pain scores, and all these other things. But has a provider really ever taken the time to say what really are your goals?

There was one PCORI project that they actually did this. They did it with primary care, and it was extremely interesting because what I saw is that the providers thought that they're going to want to get rid of their pain. And that's what I think a lot of healthcare providers think, and that's what they've been trained to do, is to heal. You help people heal, get better, and go back to a normal life. That is their expectation.

But a person with pain, what was really interesting and what we heard, people's expectation was they knew, because so many of them had been living with this for so long, that it wasn't going

Page 50

to go away, but they wanted to get back to their normal life. They wanted to be able to go fishing again, to hold their grandchild, to walk up the steps to their art studio, to drive a car.

Expectations are very different. It would be great if physicians started out, or healthcare professionals started out, by asking people, "What is your goal of treatment?" and set that goal, and work for that, and understanding, and really work as that team.

Payers don't reimburse for many of the treatments and therapies, and that's one of the problems. Even though providers may know, go to physical therapy, massage, acupuncture, biofeedback, stress management, counseling, any of those things, payers aren't reimbursing. And if people do get to go to physical therapy, they limit the number of sessions that they're allowed to have, and that's not useful.

People with pain were tapered far too fast or simply cut off without any pain management interventions whatsoever, and this was really a big

Page 51

problem because so many people were just cut off; we won't prescribe anymore. They never thought about what is this person going to do.

Just because they're not taking opioids doesn't mean they're not going to have pain. They still have pain. They still need to be able to manage that pain. It gets back to those kinds of quotes that we had, and the number of people who really thought about ending their life because of the pain, so it was really hard; or a lot of them because providers, unfortunately not all of them were trained in how to taper. A lot of them were tapered too fast, and it wasn't useful.

Many of them, what they heard was just, "You're going to have to learn to live with it," and that's something that all of us have heard living with pain, and this is something that I heard many times before I went to a pain management program. While I'm very creative and I really work hard at doing whatever I can to accomplish any task or resolve any problem, I could not figure out how to manage my pain, and I did look to healthcare

Page 52

providers.

It's sort of like this problem. I mean, it's impossible. And that's what it looks like when you tell someone to learn to live with their pain; impossible, because if you asked me to solve this problem, I would have no clue what it is and how to do it. But if I started taking classes and took some in algebra and went up to plane geometry, calculus, trig, and maybe work my way up to differential equations, and I had really good instructors, and I worked hard, and we worked together as a team, at least I could begin to understand this problem and work through it. But someone had to teach me how to do it. I just couldn't look at it and know how to solve it.

It's the same with pain. We can't expect people to just go, "Oh. Learn to live with it," and they're going to say, "Okay. I can do that." We need to teach them how to do that, and that's been the missing tool for so long, is don't tell me; teach me how to do it.

One of the problems today, if you go back to

Page 53

the '70s, is that's what we were training healthcare providers to do, that multidisciplinary approach to pain management, all of those components. We were training them. But all of a sudden that stopped and it shifted. So pain management education for all healthcare providers really focused on prescribing and procedures, and they didn't get very much of it either. In all of the education they got, an average of 2 to 6 hours was all the pain management they got.

If you look at what veterinarians get, they get 80 hours of pain management. I mean, it's great that they can take care of our critters because they can't communicate and help the vet tell them this is how I hurt; this is what I feel.

Guess what? People can't do that any better either. We really have a hard time communicating our pain. We need to be able to have better conversations be a part of the treatment team, and providers need to be able to have more education to pick up on those kinds of things.

I know that the National Pain Strategy was

Page 54

introduced right before the CDC guideline. Unfortunately, they never really got hold because one of the big pieces of that was provider education. And while it's moving forward, it's moving forward at a slow pace, but there's still so many people out there who are living with pain. Remember, they all want to feel better yesterday, and you can't just expect them to just feel better.

Healthcare providers are not paid for the time it would take to do a complete assessment, even at the acute level. So many of them are in these large practices. They have X number of minutes to spend with the patient, and that's it. So they have a checklist of what they have to do.

We need to be able to pay providers for their time to be able to make a good assessment and determine what's really best for this individual. And when it comes to any kind of medical treatment, whether it's the opioid or anything else, the decision should only be between the provider and that person living with pain and what's the best thing for them based on their medical history.

Page 55

That's the way it should be. It shouldn't be on a lot of other, well, the policy says this, because that may not fit. Remember, each one of us are individuals, and we have our own special unique needs.

One of the things that is being done is PCORI has funded a number of grants to help reduce the opioid prescribing, and many of them -- many of them -- are focusing on tapering and stopping opioids.

The American Chronic Pain Association has been involved in many of these grants. We've provided a lot of our members as patient advisors. Some of them have offered CBT, physical therapy, and shared decision making. And that's all good, but the problem is they can use one of those things.

There was only one that I know, that I worked with. It was out of a Kaiser in Oakland that actually looked at the combination of therapies along with the tapering. And they actually did groups, support groups, with people

Page 56

with a healthcare professional, and trainings every week to teach them all of the components of pain management while they were tapering them. These folks did really well because if you just taper their medications, guess what? They still have pain. You can't just taper off their medication and expect them to be better.

So the problem is that none of them combined the number of therapies and treatments that people needed to manage their pain long term. It was little pieces here and there. And that's great, it's a good start, but we need to have a comprehensive program in order to help people.

It's really important to have that complete thing because they still have pain. People with pain, just because you give them one component of that and take away another, they still have pain. And not everyone that has chronic pain needs an opioid; not everyone, but there are some.

There are some out there that even using all of the other components of pain management, they still need an opioid. They still need it. They

Page 57

need more than just tapering. They need to be taught how to manage their pain and other interventions that may be necessary. They may need surgery. There are a lot of things, both by the healthcare professionals and even through self-management. They need to know how to manage their pain.

Really what we need is a balanced approach, and that's the thing that I think, since the very beginning when I started the American Chronic Pain Association, we have never changed, the way we look at pain management. It's always been that balanced approach, combining all of the different things.

We teach a lot of different skills, and it's up to the individuals which one they need. It's not like you follow this line, or you follow this pattern, or this one. It depends on what individuals need because each of us are different. Our needs are different, our pain is different, our lifestyles are different. We each need different things, but we need to be able to offer all of them in that balanced approach.

Page 58

One of the ways that we help people understand what it means to have a balanced approach to pain management is by using an analogy of a car, except a person with pain is like a car, but their car has four flat tires. Our expectation is all we need is that one quick fix, that pill, or one treatment or therapy, and we're good to go. The problem is it only puts air in one of our tires. And it may do exactly what it's meant to do, and it's doing a great job, but the problem is we still have three flat tires. We cannot go anywhere.

So the question is, what else do we need? As I said, everybody is going to be different. It could be physical therapy; it could be counseling; it could be nutritional guidance; it could be acupuncture; it could be stress management; it could be a peer-led support group.

When people get all four tires filled, it's up to them to maintain their car. You don't take your car back to the dealer and say wash my windshield or fill her up. That's our job. If something goes wrong with the car, then we take it in for a checkup. You see, it's a combination of treatments and therapies with the person with pain at the center of that, part of the treatment team. It gets them up and gets them going.

I'm sorry this slide didn't go out right. This is our website. It's the acpa.org; that's T-H-E-A-C-P-A.org. You're welcome to visit it. We have a lot of tools, and that video, the car thing I just told you, is actually an animated video. I want to thank you for your time and your attention.

DR. CHAI: Thank you, Ms. Cowan. This is a sensational presentation. You've provided us so much insight and information. Thank you so much for really highlighting and reinforcing how important it is to get the science right, and really why we are here today and tomorrow.

Thank you, Ms. Cowan.

MS. COWAN: Thank you.

DR. CHAI: Yes, thank you.

DR. CHAI: We will now hear from Corinne Woods for an Overview of Current Applications and Uses of MMEs. What you will see is as we go through all our presentations over the next two days, the presentations will build on each other and really reinforce the science and our goals of what we're trying to achieve. Thank you.

Page 60

Presentation – Corinne Woods

MS. WOODS: Hi. Good morning. My name is Corinne Woods, and I am one of the team leads on the Drug Utilization Team in the Office of Surveillance and Epidemiology at CDER in FDA.

Today I will present an overview of current applications and uses of morphine milligram equivalents in the U.S. Some topics I will touch upon are the use of MMEs in clinical practice, as well as some state regulations which may influence opioid prescribing. I will also provide an overview of how MMEs are used in dispensing and reimbursement, as well as in research.

MMEs may be used in clinical practice, and we will hear more about this later in other presentations. Practitioners, when treating patients with opioid products, may use opioid

Page 61

conversion factors or MMEs to assist in switching or rotating a patient's opioid therapy from one opioid drug to another, or when switching between different routes of administration, as well as when adding or removing opioid therapy. The goal is to achieve adequate pain control at the same level as previous therapy without an overdose or serious adverse effect such as respiratory depression.

Another area where MMEs are used are state regulations. Forty-three states have limits on the amount or duration of opioids prescribed or dispensed. Of these, 15 states have MME-based limits as well. Some examples are a lowest effective dose; a limit of 30 MMEs per day for a patient's first opioid prescription; a limit of 100 MMEs per day for all opioid prescriptions; and a limit of a certain total MME in a prescription, depending upon the severity of the patient's pain.

Four additional states have limits that are related to MME. For example, the practitioner must check the patient's record in prescription drug monitoring program software prior to prescribing an

Page 62

opioid medication above 50 MMEs per day or as a requirement for a pain management agreement if a prescription is above 90 MME total doses. Six states require a naloxone prescription to be prescribed for or offered to patients with opioid therapy above a certain MME threshold per day.

MMEs are also used in software provided to many states for prescription drug monitoring programs. The illustration here is an example of the calculated MMEs per day over time for a fictitious patient. The software may also calculate a patient's numeric risk score to assist prescribers in making therapy decisions.

MMEs may also play a role in dispensing and reimbursement. A healthcare plan may approve or reject a prescription claim based upon either the total MMEs in the entire prescription or the calculated daily MME. A prescription above a certain MME threshold may require a prior authorization before the claim is approved, for which the prescriber submits an explanation of the clinical need to the healthcare plan.

Page 63

The Pharmacy Quality Alliance is an organization which publishes performance measures for healthcare plans, and two of these measures refer to MMEs, the percentage of patients with an initial opioid prescription of 50 MMEs per day or higher, on average, and the percentage of patients with an average daily dose of 90 MMEs or higher, occurring over 90 days are longer.

Other areas where MMEs may be used span across various types of healthcare systems. Integrated delivery networks may require that a practitioner closely monitor patients with opioid therapy above certain MMEs per day or require a consultation with a pain specialist. Different MME thresholds may exist for differing levels of pain.

Hospital systems may have policies and procedures in place regarding a patient's daily MME possibly set by a pharmacy and therapeutics committee. Also, physician groups or medical groups may have policies in place regarding MME limits.

MMEs are used in some areas of research

Page 64

regarding opioid therapy. In this arena, MMEs are intended to standardize opioid exposure across opioid moiety for the purpose of analyzing opioid doses and exposure. Sometimes these analyses assess the possible association between dose and specific outcomes, like chronic use, overdose, or adverse effects.

Examples of metrics that are used in research analyses are the calculated MME per day for prescription, the total MMEs in a prescription, and a sum of MMEs per day or total across multiple prescriptions or concurrent prescriptions for a patient.

Some consideration when using MMEs as metrics in research are related to the complexities of calculating dose when using MMEs in real-world settings. These calculations are often based upon dispensed prescription data.

Another presenter will discuss some of the challenges of calculating MMEs using algorithms based on real-world data. For example, when a patient has overlapping opioid prescriptions, is

Page 65

the second prescription an early refill in addition to the current therapy? Is a gap between two prescriptions caused by as-needed use or an interruption in therapy?

The metric MMEs per day is often calculated using a day's supply value, which is typically entered by pharmacy staff and can be influenced by the prescriber's instructions or insurance requirements. Oftentimes, pharmacy staff will select a day's supply based on maximum dose allowable.

In conclusion, MMEs are widely used in many areas of health care and research in the U.S. MMEs play a role in various prescribing limits across several states. MMEs can affect prescription dispensing and reimbursement and may directly influence patient care. Lastly, researchers may wish to consider real-world use patterns when calculating metrics involving MMEs for their analyses. Thank you for your attention.

DR. CHAI: Thank you, Corinne, for the broad overview of the many applications and uses of MMEs.

Page 66

You made it very clear that we will need to keep all these different applications in mind as we discuss the science.

We will now hear from Dr. McPherson, who literally wrote the book on opioid conversion.

Welcome, Dr. McPherson.

DR. McPHERSON: Good morning again. I'm delighted to be with you. Thank you for inviting me.

DR. CHAI: I think you have a bit of an echo.

AV TECH: No, she doesn't. That was another participant who was unmuted.

DR. CHAI: Oh, okay. Thank you.

Sorry about that. Go ahead, please.

DR. McPHERSON: Okay. Take 3. Here we go again.

Presentation – Mary Lynn McPherson

DR. McPHERSON: Thank you so much for including me in this meeting. It's a pleasure to be here with you.

As you know, my name is Lynn McPherson, and

Page 67

I'm a professor at the School of Pharmacy, and my practice is primarily in hospice and palliative care. I practiced my whole career in ambulatory care as well, and I'm very much interested in opioid conversion calculations.

This is my objective, my goals for this morning and the time we have together, to give you a brief history of opioid conversion calculations and talk a little bit about the problems with doing these calculations, a new paradigm that I have recommended in a second edition of my book. Then at the very end, I'm going to share with you some late-breaking data from research in my hospice, looking at a 10-year history of the use of opioids in this population.

Well, I think by now we all know what MME is, morphine milligram equivalent, and Dr. Woods just did a great job talking about all the scenarios where we would need to calculate an MME. In my world, it's primarily patient care, which we'll talk more on the subsequent slides. But I think several of the speakers who preceded me have

Page 68

talked about the guidelines and the state limits, which speak more to trying to limit the harm caused by the opioid crisis. We hear that over a hundred people a day die from an opioid overdose. I'm not so sure how much it's the miscalculation that's involved there. I think, certainly, that's a multifactorial issue by all means.

Certainly, when we are looking at, for example, the CDC's intent guideline and state limits, the MME limits are intended to help clinicians make safe appropriate decisions regarding changes to opioid regimens, I think there's way more to it than, obviously, just an MME if that's what you're looking for.

Certainly, the MME per-day metric can hopefully be used as a gauge of overdose potential, certainly indicating those patients where maybe the clinician needs to up their game a little bit in terms of closer monitoring, or reducing, or tapering opioids if it's clinically appropriate, and certainly prescribing naloxone if it's appropriate and any other risk mitigation

Page 69

strategies that would be appropriate to implement.
I'm not as convinced that the MME per day can help predict the likelihood of addiction but certainly I think everyone needs to be mindful of, as we increase and increase the dose of an opioid, most importantly is the patient functioning better. I know we even run into this end-of-life care where sometimes clinicians are stumped and thinking, "Why is it not working? I keep increasing the opioid." Well, maybe it's not even particularly opioid responsive pain. Maybe you're completely barking up the wrong tree; or it could be tolerance; or it could be opioid-induced hyperalgesia. It could be diversion. So it could be a lot of different things going on.
In my world, this is mostly the reason why I'm asked to help with switching from one opioid regimen to another. The first is lack of a therapeutic response. Just because a patient doesn't adequately respond to the first opioid you select, it doesn't mean that they may not have a better response to a second opioid you could switch

Page 70

to.
Certainly, another one is the development of adverse effects. The classic example is someone who's on morphine and they start to itch like crazy. Well, most practitioners are going to reach for an antihistamine because that is a histamine-mediated response, but my preference would be to just switch to a different opioid instead of using a drug to treat drug-induced illness.
In my world in hospice and palliative care, huge is change in patient status. If we have someone at home on hospice and they have a pain crisis, we may need to bring them into the inpatient hospice unit and switch them to a parenteral opioid infusion, for example, to get that pain quickly under control; or whether it's acute pain, or a patient who now we've gotten them controlled in that inpatient unit and now they're ready to go home because their pain is controlled, switching back to an oral route of administration, for example.

Page 71

In other considerations, opioid or formulation availability, we certainly have had many shortages in the past years, so that's certainly something that we've had to wrestle with.
My slides keep jumping around here. I'm not sure what the deal is. Okay. Here we are, back where we should be.
Formulary issues. For example, if someone comes into my hospice on a branded opioid, we're going to try and switch them to an opioid that is on our formulary. Then of course we have patient and family healthcare beliefs. Sometimes they're more comfortable with one opiate than another.
I don't really care what you call this practice, whether it's opioid rotation, opioid substitution or switching, you're going to be rolling up your sleeves and doing an opioid conversion calculation.
That was all a preface to, here are the two questions on the table. It's either, if I'm starting with opioid A at dose B, what dose of opioid C do I need to prescribe to have the same

Page 72

analgesic effect? That's where I am in my world. The other question is, if my patient is taking an opioid other than morphine, what would be the equivalent milligrams as morphine per day, and does the exceed recommended or mandated guidelines? So those are the issues we're talking about here.
Others will be talking in greater detail later in this two-day conference, but just a little bit of background, what goes into the equianalgesic conversation? Well, the first definition is opioid responsiveness, which is the degree of analgesia achieved as the dose is titrated to an endpoint defined either by intolerable side effects or, Eureka, the occurrence of acceptable analgesia. That talks about how responsive the patient was to that particular opioid regimen.
Potency gets to the intensity of the analgesic effect of a given dose, which is highly dependent on access to the opioid receptor and binding affinity. So we've come up with this terminology that equipotent is an equianalgesic effect.

Page 73

But I do want to point out this does not necessarily imply equivalent harm. You could use one of these opioid conversion charts and do an impeccable job with the math, and come up with an equivalent equipotent, equianalgesic dose of the second opioid regimen, but the harm may actually be higher because you've made that conversion based on that ratio. So this whole practice is equianalgesic opioid dosing.

Another term is bioavailability, the rate and extent to which the active ingredient or moiety is absorbed from the drug product and becomes available at the site of action.

Mostly we talk about oral bioavailability. You can look at morphine. We say it's about 30 to 40 percent. So if someone takes 10 milligrams of oral morphine, when you take a drug by mouth, it goes down and gets absorbed from the GI tract. The first place it goes is into the hepatic circulation.

So 10 milligrams cruises in. The liver thinks Domino's delivered pizza for lunch and,

Page 74

holy-moly, if you're lucky 3 to 4 milligrams makes it out of the liver alive to be able to go to the central nervous system and do its thing to treat the pain.

But as you can see, there's a very large range in oral bioavailability with morphine. Hydromorphone, look at that range. Holy moly! It's really about 50 percent, which I'll show you again on a subsequent slide, but tremendous variability. Oxycodone has pretty high bioavailability; oxymorphone pretty low.

So here is the $64,000 question. Where does opioid equivalency data come from? Does it come from the bottom of a deep dark hole? I don't think so. Certainly we're more scientific than that.

So I was actually curious where did the CDC get their chart from. They use a conversion factor approach, where you take the number of milligrams the patient's on, you'll look up the drug on his chart, and you multiply by the conversion factor, and that would be the MME.

Where did this come from? If you look at

Page 75

the red arrow, this came from an article. It was adapted from Von Korff, et al., so I decided let's take a look at this. But when you look at this data, just simply looking at this -- before we go on -- this brings up a couple of red flags, with methadone in particular.

I can only assume that when they came up with the 4, the 8, the 10, and the 12, depending on how much methadone the patient was on, they looked at data that's been published going from oral morphine equivalents to methadone, and it was never investigated or intended to be used in reverse. So I don't think we can automatically assume bidirectionality here.

And, my girl, methadone -- while I do love me some methadone, professionally, not personally -- has no sense of humor. So if you make a mistake with methadone, you are looking for trouble.

Also, when you look at dual-mechanism drugs -- for example, tapentadol is included on this chart; tramadol is another example -- you have

Page 76

to ask yourself, "Self, how much of the pain-relieving effect of tapentadol is due to inhibiting norepinephrine reuptake?" And with tramadol, it's serotonin and norepinephrine.

So I think we have to consider binding to the mu receptor versus the other probably much larger clinical effect of these dual-mechanism drugs. What's the scoop there?

So anyway, I went to this article by Von Korff, et al., and this is the chart that they have published there, and they state that, "The conversion factors were based on information from multiple reference sources, 16 through 20, and after reviewing published conversion factors, consensus was reached among two physicians with clinical experience in pain management and a pharmacist pharmacoepidemiologist."

That's interesting. I feel like I'm from Missouri; show me. I went to references 16 through 20 and I tried to find them. For example, the Oregon Health Sciences University Chronic Pain Manual, I couldn't even find it. Most of the rest

Page 77

of these were kind of tertiary references. So basically, Von Korff was a tertiary reference of tertiary references, and then the CDC embraced those.

So, you know, it kind of really boils down to the burning question.

This really boils down to the burning question. Are opioid conversion calculations set in concrete? I know that my pharmacy students when we talk about drug math, they're so excited because they think, "Oh, my gosh. Drug math is one right answer." And in so many areas of drug math and pharmacy, that is true; there's one right answer. But, you know, I think when we talk about opioid conversion calculations, I think we're on a little bit shakier ground. I don't think it's quite that cut and dry.

So as you heard from the kind introduction, I did write a book on opioid conversion calculations. This is the cover to the first edition, 2010. And as you'll see, the chart that I recommended at that time is very consistent with

Page 78

what the CDC is using. I went along with the flock because, frankly, at that time, in 2010, this was the best evidence, really, that we had. But I did spend the rest of the book talking about it's not just about setting up this ratio, and even that freaks out a lot of people. So if you're really freaked out about that, let's call a third grader, and they'll do that for us.

That's not why we went to medical pharmacy nursing school or whatever professional school we went to. It is so that we could critically think through this process and consider all the variables typed here: the heterogeneity of opioid receptors; the quantitative difference in metabolic enzymes from person to person, anywhere from an 11 to a 30-fold difference from person to person when you talk about the cytochrome p450 system; so complete and total variability of the pharmacokinetics and pharmacodynamics of opioids.

Not to mention the difference in opioid responsiveness in different types of pain. I mean, opioids are not always the answer in neuropathic

Page 79

pain; it's only partially responsive. I think a big one for me is where the heck did this data come from? As a matter of fact, we're very excited to be launching a PhD in palliative care this fall. We're planning our first course, and part of that is looking at where did hospice and palliative care come from, what are the origins, where are we now, and what does the future look like?

I had the opportunity to speak with Dr. Robert Twycross from the United Kingdom. I understand the UK is on the line here today. He is absolutely brilliant. He posed a question to me and, whew, thank goodness I knew the answer.

He said, "Do you know the really early charts of equianalgesia said that 10 milligrams of parenteral morphine was equal to 60 milligrams of oral morphine. So why do all these charts today run around saying it's 10 and 30?" I said, "Because when people first thought that 10 to 60, it was based on a single-dose study."

If we take any one of you today and give you some painful insult, and say 10 milligrams of

Page 80

parenteral morphine would be necessary to adequately treat that pain, and we all came back next week at this time and gave you the same painful insult, that would take 60 milligrams. But we've since learned that with chronic dosing, the sixth glucuronide metabolite actually is a super spinal analgesic, so really it's closer to this 10 to 30.

So single-dose studies, multiple-dose studies, it's drawing from pharmaceutical industry, and it's certainly my personal impression that when a pharmaceutical manufacturer publishes and they're prescribing information, an equianalgesic recommendation to convert to their product, they're being conservative because they don't want to harm anybody either. But it was never their intent that you use their equianalgesic guidance to go to their product to use it in reverse; so lots of different sources here.

Nowhere does this chart consider patient-specific variables, so if the patient has comorbidities; do they have renal impairment;

Page 81

hepatic impairment; are they young; are they old; are they skinny; are they fluffy? What's the scoop? Other medical factors.

The big question is, do we have bidirectionality? I just mentioned my concern about the CDC guidance. With methadone in particular, I do not think that it's taking into consideration bidirectionality.

So I did the second edition that came out very late in 2018, and I made a few tweaks to the chart. As you can see here, morphine, 10 milligrams parenteral, which includes IM, IV, and subQ because it's close enough for government work, although I think an IM opioid should be voted off the island. Instead of being 30 milligrams of oral, I bumped it down to 25, and we will talk about that.

I have to tell you, there's been tremendous uptake of this new chart with the notable exception that people whine audibly that they can't divide or multiply in their head by 2 and a half. Again, call the third grader.

Page 82

The big, big change is looking at hydromorphone. Hydromorphone from parenteral to oral is really 1 to 2.5; it is not 1 to 5. And consequently, based on excellent data now, 2 milligrams of parenteral hydromorphone is about 25 of oral morphine, as it's not really a 20 to 1 ratio. This has been kind of a wake-up call for a lot of people.

So let's look at some of this data. What is the deal, first off, with the IV-to-oral morphine? We've had 10 to 30 for probably 30 years, so how dare I make it 1 to 2.25 or 10 to 25. Actually, the data does support that the equianalgesic table with this ratio is anywhere from 1 to 2 to 1 to 3.

Kalso in 1990 showed that 20 or 30 of morphine by mouth was about 10 milligrams IV or subQ. Starlander in '11 said it works out to 1.1 to 2, but that was only 11 patients so I can't get too misty over that. Takahashi in 2003 said, well, somewhere between 1 to 2 and 1 to 3, based on a lot of patient-specific variables. And I'm very fond of, as you'll see in a moment, the practice of

Page 83

what they do at MD Anderson Cancer Center, because they do this all the time. They see 10 milligrams of parenteral morphine is 25 of oral morphine.

As you can see, this is an abstraction from the chart that I used. I am arguing that 10 milligrams of parenteral is 25 of oral. That's not to say that 10 to 30 is incorrect. Frankly, sometimes I'll even do the one-third if I'm on the fly because I know I'm going to probably do a dose reduction, or perhaps it works out that way to get to the next reasonable dosage formulation or tablet strength.

Alright. So what's with the morphine-oxycodone thing? We've always said for 30 years, 30 of morphine is about 20 of oxy. What's the deal? So does 25 of morphine work out to be 20 of oxy? Can I do that? Am I going to go to jail? What's the scoop?

We do know that there's tremendous variation, as I showed you several slides ago, in the bioavailability of these drugs. Morphine, in particular, is highly variable. Oxycodone is

Page 84

60 percent or more. On average, it's about 80 percent. So really, you will find charts that say oral morphine or oral oxycodone are exactly the same potency. It goes anywhere from 1 to 1 to 2 to 1. Really, it just depends on the patient's ability to absorb the opioid. So I'm very comfortable with 25 of morphine is about equivalent to 20 milligrams of oral oxycodone.

Alright. What about this one? This is a big one, parenteral oral hydromorphone. Really, this is a whole question of bioavailability. And if you look at super old data, 1987-1988, it's about 50 percent. Now, I will grant you there was a very large degree of variability when you look at the bioavailability, so we have to keep that in mind. But it's really not that 5 to 1; it's closer to 1 to 2 and a half, as shown in my chart here.

So do we need to evaluate the conversion from oral to parenteral? No, I would argue because, really, it's determined by the bioavailability, and secondarily by pharmacogenetics. Clinical guidance in large

Page 85

patient populations has provided average guidance with the best being 1 to 2.5 with IV to oral.

This is probably the biggest game changer that drove the changes I made in the recommended chart. This is data from my very dear friend, Akhila Reddy, who's a physician at MD Anderson, and she really did a very fine job with this research looking at many, many patients at MD Anderson, retrospectively; patients who had been on IV hydromorphone, and what would be the equivalent if we switched to either oral hydromorphone or on morphine or oral oxycodone. She did see some biomodal distributions here, 1 milligram of IV hydromorphone. If the patient was on less than 30 milligrams a day of IV hydromorphone, it turned out to be 2.5 of oral.

So that is exactly what I've reflected in the chart. If it's greater than 30s, it's a smidge or less, which I keep in the back of my mind. If you're going to oral morphine, it came out to a little more than 11 and a half or so, unless they're on a very high dose, and then she also did

Page 86

it for oxycodone.

So her bottom line, if you look at the bottom left of this slide, 1 to 2.5 IV-to-oral hydromorphone. They used the 1 to 10, which they've used historically for years at MD Anderson. I made it 1 to 12 and a half to make the chart work, and then 1 to 8 for IV hydromorphone to oral oxycodone.

I don't know. If I write a third edition to this book, will I even have an equianalgesic chart? Should it be a ginormous chart where you go over a row and down a column, and it's a very specific ratio for that particular opioid you're coming from and to, and dependent on the route of administration? I don't know. But I tend to think that might confuse people even more.

So I really did struggle very hard to keep the equianalgesic chart to make it the safest and the easiest for practitioners, and of course patients is the bottom line.

So here's the elephant in the room. What about the morphine hydromorphone? What about the

Page 87

bidirectionality issue here? Is it bidirectional? If you go from IV hydromorphone to oral morphine, is it the same if you're going in reverse?

One study by Lawlor looked at subQ to subQ hydromorphone and morphine, and back again, and oral to oral. So when you're going from morphine to hydromorphone using the same route, regardless of which it was, it turned out to be about 5 to 1. When you're going from hydromorphone to morphine, it was closer to 4 to 1.

But even Lawlor in that study said, "Look, this data is highly skewed and variable. It's not at all normally distributed." So they argued that this data was not clinically significant, the small difference we saw in bidirectionality.

Then I'll get this question once in a while. Okay. If you're switching somebody from 10 milligrams a day of IV hydromorphone to oral morphine, and you use the old chart -- which, I got to tell you, most people still use -- it calculates out to 200 milligrams of oral morphine.

So if your mama is getting 10 milligrams of

Page 88

IV hydromorphone and it's time to go home, are we really going to put mom on 200 milligrams of oral morphine? Or if you look at the next column over, you could use what I'm proposing, which would be the 2 milligrams of parenteral hydromorphone, which would be 25 or oral morphine, it works out to 125 milligrams of oral morphine.

So you would say, well, the new conversion is more conservative, and I would argue is very much more consistent with Dr. Reddy's data.

Now, what about switching back? If someone is on 200 milligrams of oral morphine and you need to switch them to IV hydromorphone, the older method would say that's only 10 milligrams, of course, because we're doing it in reverse, but the newer method would say 16. So the new conversion seems more aggressive, obviously, than the older conversion ratio.

But I would argue there is more than one way to pluck a chicken. If you take 200 milligrams of oral morphine, we have pretty good data that going from oral morphine to oral hydromorphone is a 5 to

Page 89

1 ratio. So if you take 200 milligrams of oral morphine, that's going to be 40 milligrams of oral hydromorphone, which if you look at the bioavailability data of hydromorphone is 16 milligrams of IV hydromorphone. Boom! So that's how I came up with these numbers.

What do I think about this chart? I think the chart that I have proposed here is about the best you can do with what we currently know. But I always say -- when you say what's the magic dose -- it's sort of like saying which one is my seat?

I don't know. My job was to get you in the ball park. Your job is to put on your big-girl pants here and use that big old brain of yours, and all that critical thinking that you learned about in medical pharmacy, nursing school, wherever you went to school, and look at your patient and think through what do I do with this number. I mean, you calculate a number. You can either go with that number. You can increase it or you can decrease it. So I think you have to use some critical

Page 90

thinking skills.

So here's the big question. Have practitioners gotten their arms around this practice? Well, let's take a look. This is one of my current residents, Dr. Cindy Ngyuen. This was one of her two projects this year, and I think she did an awesome job. This was an online survey. I love the title even. It's called, Not So Surprising: The Inconstancy -- I love that new word -- of Oral Morphine Equivalent Calculations.

So again, this was an online survey to self-reported healthcare clinicians who dispense, administer, or prescribe opioids. The aim was to explore the practices, perceptions, and potential barriers to perform safe and effective opioid conversion calculations to calculate a patient's total daily oral morphine equivalent. We called it OME.

We had 406 people respond. We were really tickled. As you can see, 28 percent were advanced practice providers; 17 percent were RNs; 34 percent, pharmacists; and 22 percent were

Page 91

physicians. The respondents reported 99 percent of them said, "To be able to accurately calculate an OME is highly important," and 94 percent said they were strongly confident in their OME calculation.

The study was actually much larger than what I'm reporting here, but I'm just giving you the highlights. We asked them about which of the following is a barrier, in your opinion, to performing a safe and effective and a highly accurate, highly important calculation?

As you can see here, 51 percent said, "Finding the best equianalgesic data is a problem" in a little over half of the respondents; clarity on when to dose-reduce the calculated dose, again, a little bit more than half struggled with that; confidence in the accuracy of an online calculator, again, a little more than half. Personally, I think that should be a 101 percent.

What about particular opioids? What do you do with transdermal fentanyl? What do you do with transdermal fentanyl if the patient weighs 80 pounds? How about my girl methadone? How about

Page 92

somebody on a ridiculously high dose of an opioid?

I know working in hospice, we often get patients referred to us because the other healthcare team, they don't know what to do anymore. We get somebody on 30 milligrams an hour of IV dilaudid and it's not working, we don't know how to fix it, so they turf the patient to hospice.

The last is uncertainty of the patient's medication adherence. I've certainly been burned by that, where we had one patient, an older woman, and her son was taking care of her. He reported to the nurse what he was giving his mother, which was a PRN morphine dose.

The nurse asked me to do a calculation to methadone. I did it, and the older woman became very, very sedated and was on the road to flat-out toxicity, only to find out the son had made all of that up because he didn't want the nurse to think he was a bad son. So, great. I almost killed the patient because he didn't want to look bad.

Then we asked them how often do you do a calculation. Forty percent said daily. Another,

Page 93

almost 30 percent, said weekly, and then it trailed off from there. We only asked one question that really got down to where we could compare how people do things differently. We said, now let's see. Let's say you write or are handed two prescriptions, morphine extended-release 30 q12 and immediate release 15 with an order for 1 tab q4 as needed PRN.

So how would you calculate the total daily dose of morphine here? Would you, A, say it's 150 a day based on using the extended release as scheduled and all of the allowable immediate-release morphine PRN doses; or would you say I'm just going to count the schedule because I don't know how much of the MSIR they're going to use; or would you eyeball the patient and say, "Well, in my professional opinion, I think they're obviously going to use the extended release, which is scheduled, but this is how much of the immediate release I kind of think they're going to use."

This was split a third, a third, a third. . I know insurance companies, you have to go with

Page 94

option A, but you can see where this could really get you into trouble in terms of patient care. So if you go with option A, which is what the pharmacy has to do for insurance purposes, it could throw it over one of these arbitrary state limits, when in fact that patient may be option B, and they don't use any of the immediate release for PRN dosing. So this really has significant patient care implications.

Alright. This was a study -- Dr. Jeff Fudin is speaking today. His resident and my resident did this survey where we also did a survey on social media advertising to professional organizations. 319 participants took the study, and we asked them simply, look at these 8 prescriptions right here, these 8 opioids with a different range. Could you tell us -- just type it into the box -- the estimated morphine equivalents?

So we did hydrocodone, 80; transdermal fentanyl, 75; methadone, 40; oxycodone, 120; and hydromorphone, 48. And as you can see here, there's quite a bit of variability.

Page 95

Transdermal fentanyl, 75, if the patient had normal body habitus, I would say that's somewhere between 150 and 180 milligrams of oral morphine equivalents per day, so that's right in the ball park, 176. But 118, that's a pretty big range you're looking at there.

Hydrocodone, I think the whole world thinks hydrocodone and morphine are pretty much the same, so 88 is pretty darn close to 80. But still, plus or minus 50 percent, that's a pretty darn big range; hydromorphone.

Look at methadone and oxycodone; wow, a big range there. I think that's pretty considerable. I think transdermal fentanyl and the methadone, in particular, you can see quite a bit of variability.

Alright. This is data provided, again, from my friend Dr. Reddy, who is presenting it at the MASCC Conference, like now I think it is. I was part of her study where we -- again, this is another survey, but what's nice about this is this is an international survey looking at opioid rotation, which was defined as substituting one

Page 96

opioid entirely with a different opioid; so going to a different molecule altogether versus an opioid conversion, which is sticking with that opioid but using a different route of administration.

We did have various scenarios, which I'll show you in a moment. And talk about a nice capture of data here, 370 responses from 53 countries. I'm not going to read this to you, but I'll just let you kind of take this in.

This is looking at those conversions and the opioid rotation ratio. For example, the first one is from IV-to-oral morphine. 349 people answered that. Everybody's comfortable with that one. The median response was 3; the interquartile range, pretty tight, from 2 to 3; and the mode was 3. So everybody's pretty comfortable with that one.

IV-to-oral hydromorphone, this is interesting. We see a wider range here. The median was 3 but the mode was 5, so that's kind of interesting.

Again, I'm not going to read this. You'll have the slides in a short period of time. This is

Page 97

interesting, though, looking at the international flavor here. It's not consistent across the board. Morphine's pretty tight. IV-to-oral morphine, in the U.S., the median and the mode is 3; in Canada it's 2 and 2; in the UK it's 2 and 2. So I feel like a big winner because I went with that 2.3.

As you can see, there's a big difference in the U.S. We say IV-to-oral hydromorphone is a 1 to 5 ratio when in fact Canada and the United Kingdom, where we had the next most highest responses, they were very tight, 2 and 2, which again in my chart I have 1 to 2.5. So me and Canada and the UK, we are tight. We got it going on. So as you can see, there's a lot of variability cooking with this.

Alright. So I know you're sitting there thinking, "Why are you banging your head on the table?" There's an app for that. Of course, there's an app for that. There's an app for everything.

I remember years ago I had a pharmacy student on rotation with me, and we just wrapped up team meeting, and one of the nurses said, "Hey.

Page 98

Could you do this calculation for me?" And I said, "Oh, this is great for the students." So I turned to the young man, and I said, "Could you do this calculation for the nurse?" And he said, "Oh sure. I've got an app for that," and I said, "Of course you do."

So he goes through the math, and I hear him inhale sharply, and I said, "What's the scoop?" And he said, "Wow! This is unbelievable." I said, "What did you come up with?" He said, "It's like almost a million milligrams of morphine." I said, "Well, what do you think of that number?" He said, "Well, I think we're going to have to order more morphine."

I cannot make this stuff up. So clearly somebody disengaged their brain, so what do we think about online conversion calculators?

This is a very nice study looking at a variety of calculators, and as you can see in the blue box, across the top we see six or seven different online conversion calculators, and going down in the columns, we have different features.

Page 99

So all but one do the opioid calculation for you. Not all of them share the data that informs their algorithm by giving the equianalgesic table. Not all of them will let you convert from multiple opioids as we frequently do. Only two of them account for acute and chronic dosing with morphine and methadone, and transdermal fentanyl, buprenorphine, methadone, tapentadol, not included routinely in all of them.

Here's a big one for me, the ability to dose-reduce because of incomplete cross-tolerance. That's critical in my opinion. Then a couple of them, most of them, half of those I guess are available for a smartphone.

So this study is also looking to compare and contrast these calculators; identify the mathematical disparities; and compare automated conversions against manual calculations revealing potential risks and making recommendations. As you can see, the variation range is from minus 55 percent to 242 percent. Wow! That's amazing.

As I said just a moment ago, at my

Page 100

university we offer an online master of science degree in palliative care, and actually as we speak, we are in week 2 of PALC 615, which is the advanced pain management course, and we just last week did this exercise.

But this is data looking at variability among online opioid conversion calculators performing common palliative care conversions. This study -- which we're just now responding to reviewer comments, and I'm pretty sure it's going to be published, accepted for publication, when we're done that -- we looked at the cohort of students. It was about 50 students each summer in 2018 and '19 and how they handle this.

The way the discussion question went was, first, what do you think of online opioid conversion calculators? Second, here are three hypothetical problems -- and again, I just want to point out the problem, that these are not about the therapeutics, like, "Oh, I would have added a steroid instead," it's all about the math -- and take these three problems; find any three opioid

Page 101

conversion calculators online; run these three scenarios; and record your results.

The next question is, what do you think about how these calculators did from calculator to calculator? And the last question is, now what do you think about online conversion calculators?

Here's the data. As you can see the three cases, the first case is a 78-year-old woman getting transdermal fentanyl 75 mcgs. The patient doesn't seem to be responding despite dose increases. She is 5 foot 4 and weighs 82 pounds. And again, this is a program for people getting a master's degree in palliative care. We have people getting palliative care and on hospice who are 5 foot 4 and weigh 82 pounds, so if you don't ask about the body habitus, you are not doing your job.

The ask was to convert to long-acting oral morphine and determine a dose of short-acting for breakthrough pain. So in each of these scenarios you will see the first one is the record value, which is what we calculated, and you'll see three numbers. For example, you see 40, 60, and 80

Page 102

there.

So again, 75 mcgs would be about 150 to 180 milligrams of oral morphine equivalents, but because this patient is cachectic and we know that you nowhere get the bang for the buck you would expect, we empirically reduce it. So the best answer would probably be around 60 milligrams of oral morphine.

But then we did our own little interquartile range kind of deal empirically here and said, "Well, anywhere between 40 and 80 we would consider as being in the range." But then if you look at the most popular conversion calculators like Practical Pain Management; GlobalRPh; ClinCalc; the Oregon one; Agency Medical Director's Group, look at the range. Holy moly! There is huge disparity there.

The second one was a 58-year-old man with end-stage lung cancer getting IV hydromorphone at 6 milligrams an hour, and we see this all the time. He's using his 3-milligram bolus about 3 times an hour, so this guy is getting 15 milligrams an hour,

Page 103

on average, of IV hydromorphone. And the pharmacy just called and said, "Well, you used the last drop of IV hydromorphone in the entire state; you're going to have to switch."

So the patient can swallow, so let's switch him to oral morphine. So it calculates out to about 3600 milligrams of oral morphine, but as you can see, our reference value in the middle is 2250 because we did reduce for cross–tolerance; so in the center there, that's about a third reduction, but then we have our two endpoints as well. But you can see in the next calculator, it's all the way up to 6,000 milligrams. That's the range we saw from the students.

The last one is a patient on MS Contin and MSIR. The pain seems to have a neuropathic component, so we want to convert to oral methadone, so we use very straightforward conversion. But as you can see, look at the Oregon one; quite a bit of variability with that.

The last thing I want to share with you from this study is, looking at dosing and reduce

Page 104

tolerance for all these scenarios, if you'll look at the dosing of the immediate release, 5 percent wanted to give the immediate-release opioid longer than every 4 hours, and half of them said every 4 hours.

Looking at cross-tolerance in scenario number 1, which is the transdermal fentanyl, 60 percent wanted to reduce for cross-tolerance when in fact the data and form is really that's not necessary, and the same with scenario C. So it's kind of all over the place with this as well.

This is the five-step process that I argue is a good way to go when doing an opioid conversion calculation. It was part of Arnold Gammaitoni's study here years ago. We published this in 2003.

When someone calls me, I really do these five steps. When a nurse or a doctor calls me, I'll say, "Tell me about the pain," because sometimes the answer is, "You don't even need to do a conversion calculation. The patient has screaming metastatic bone pain. Have you thought about adding a nonsteroidal or a steroid to help

Page 105

with that pain?"
So assess the patient's pain. Is even an opioid the correct drug to be using? Let's start at the 20,000-foot view. Then I want to know certainly about the severity, because when I get down to step 4, I need to know was the patient in pain, was their pain controlled, and maybe we're switching because of the side effects. You need to know about the patient's pain.
So you're determining if the situation is uncontrolled pain, worsening of the pain, is it a new kind of pain, and maybe you need an adjuvant drug because it's neuropathic.
The next is to determine the total daily use of the current opioid. This should include all scheduled, all long acting, as well as an average utilization of breakthrough.
All the time, nurses will call me and say, "This guy's on MS Contin 60 q12 and 20q2 PRN." I say, "Okay. How much are they using in the PRN?" I just told you, "20q2." I said, "No, you told me the order. You did not tell me what the patient is

Page 106

getting on average."
Once in a while, it will be, "Well, I don't know. They're being discharged from the hospital. They came right here from the hospital. How can I tell?" I said, "You pick up the phone and you call the nurse in the hospital where he came from, and if you can't get that data, the PRN, I don't include it in the calculation."
Now the reason 3 is in black is because I do believe an online calculator can do number 3 for you. After you decide what you want to switch to, this is a simple ratio. This is the third-grader step here. I do believe the online calculator can do a nice job saying if 20 of this is 25 of that, then 40 of this has got to be X, Y, Z, so I'm trusting the computer to do that.
But then I really don't trust the computer to do step 4 or 5, similar to step 1 and 2. The computer spits up this number. So again, as I said a few minutes ago, you can either run with that number, rarely will we increase that number, or often I decrease that number. So it depends on the

Page 107

situation.
If the patient's pain was very well controlled on the current regimen and I'm just switching formulations, and it's not a new molecule, I'll probably just round down to the next most convenient dosage formulation; what tablet strength is it, is it available in, for example.
If I'm switching drugs, entirely switching opioids, if they were not in pain and I'm switching because of a side effect, I might cut back 50 percent because of lack of complete cross-tolerance. If they were in pain, I'm not going to cut back quite that much. Maybe I'll do a quarter; maybe not even that much. It just depends.
Step number 5 is to monitor your patient like nobody's business, and you know no online calculator is going to do that. They just walk away. They're done. They're out of here. So you follow the patient very carefully. As a matter of fact, with methadone, we have a policy in the hospice I work with that the nurse must visit every

Page 108

day for the next 5 days and go through the laundry list of monitoring parameters to make sure the patient is not developing toxicity.
If you don't see methadone toxicity it's because you're not looking, because methadone does give you fair warning. I know everybody snores, but when the patient starts sucking the curtains off the walls, this is a sign that all is not well.
So those are the five steps that I think are very important and, again, an online calculator will only do step number 3 for you. And since I'm a hospice girl, I just wanted to share with you, for fun, some of the data.
I have a huge database of data from a very large hospice in the United States. We have a database of every drug prescribed for a hospice patient admitted to the hospice and the discharge by death, which is about 85-90 percent of those patients, over a 10-year period, 2010 to 2019.
We specifically looked at patients who were prescribed an opioid, which is 137,000 patients. The length of stay, our mean length of stay, is

Page 109

51 days; the median is 10 days. This is a problem with hospice today, is patients being referred and the hospice nurse hopes that they can get through the 4-hour admission visit before the patient dies. So I really wish we would all row in the same direction so that we could get patients in the hospice earlier, and they could really enjoy the hospice benefit.

Anyway, I have got a ton of data, but I just wanted to share this with you, looking at the blue, which is at the time of admission, and the red is at the time of death. Again, our median length of stay is 10 days, but our mean is 51 days.

I just arbitrarily came up with these MME buckets of less than 50 milligrams, 50 to less than 90, 90 to 199, and then I added 200 to 400 and over 400. So on admission, less than 50 was half the patients, 50 to 90 was 17 percent, and so forth.

If you look at the time of death, 50 percent are still under the 90, but 90 to 199, and probably most of them are toward the lower end, that's

Page 110

25 percent of patients. And we still have a nice little chunk of people on higher than 200 milligrams or even 400 milligram, or a morphine equivalent. I'm here to tell you, if you don't do hospice for a living, I promise you, some people die very, very hard. It can be very difficult.

So in closing, what's the plan, Stan? I think we all have to be Boy Scouts here; okay, maybe a Girl Scout if you want to be fair balanced. I think there is so much more to opioid conversion calculations than the simple calculation itself. And don't get me wrong; I do love drug math, obviously, but I think we have to do a very careful assessment.

Number one, is an opioid even really the best treatment for this patient, and to use the very best equivalency data that we can, that is based on science. I think mine is pretty awesome, but then, again, I would say that. But just use something that is fair balanced. I would not use a pharmaceutical industry's guidance in reverse from what they intended. I would never do that.

Page 111

The rule I roll with all the time is I'm very conservative with the schedule dose, but because I'm dealing with hospice patients, I tend to be crazy generous with the breakthrough dose. If it's an ambulatory patient with chronic non-cancer pain, the provider may choose to not even provide a PRN. It just depends on the clinical situation, or they may say you can take a Percocet every 4 hours as needed but not to exceed 2 tablets a day. That just depends on the clinical scenario.

I think we should be treating patients, not numbers. I think we should be vigorously monitoring the patient response, and I think we have to be very, very careful in those states that do have some arbitrary MME limits to consider how this will impact patient care. Thank you so much for your attention. I appreciate it.

DR. CHAI: Thank you, Dr. McPherson. That was, frankly, amazing. You're a phenomenal speaker, and that was a tremendous amount of information that you've jammed packed into that

Page 112

time.

We're actually a little bit ahead of schedule, so we're going to go ahead and take a 10-minute break. When we return, we'll be hearing from Dr. Fudin.

Dr. Fudin, will you be ok to start 10 minutes early, at 11?

DR. FUDIN: Yes, I will. Can you hear me ok?

DR. CHAI: Yes.

DR. FUDIN: Okay. Yes.

DR. CHAI: So we're going to adjust a little bit in order to provide more time for either presentations or clarifying questions. Please plan to be back at 11 a.m. Thank you, everybody, and please remember to mute your phones.

(Whereupon, at 10:51 a.m., a recess was taken.)

DR. CHAI: Welcome back, everybody. I'd like to welcome Dr. Fudin, who has many years of experience in pain management and has published many articles in this space.

Page 113

Of note, Dr. Fudin will not be able to join us tomorrow for day 2. Panel members, please jot down any clarifying questions that you may have for Dr. Fudin today, as well as for our other speakers, to ask during the first clarifying question session today at approximately 12:10 p.m. Thank you.

Dr. Fudin, go ahead, please.

DR. FUDIN: Thank you, Grace. Can you hear me ok?

DR. CHAI: Yes, I can. Thank you.

DR. FUDIN: Fantastic.

Presentation – Jeffrey Fudin

DR. FUDIN: The topic I'm covering today will be Individual Patient and Medication Factors that Invalidate Morphine Milligram Equivalents. This next slide is a disclosure slide to show you various companies that I've worked for as a consultant. I do have to add Chempharm, which is just recent, and Collegium, which is just recent, after these slides were submitted.

The objectives, at the completion today, hopefully you'll be able to explain opioid

Page 114

conversion calculations and strategies when developing a care plan for patients in chronic pain; assess patient-specific factors that warrant adjustment to an opioid regimen; identify important drug interactions that can affect opioid serum levels; and describe how pharmacogenetic differences amongst patients can affect opioid efficacy, toxicity, and tolerability.

This next slide is really especially important. This slide delineates the various opioids by chemical class, and there are a few things I would like to point out here. First, is that if you Look in the first column of phenanthrenes, most of the commonly prescribed opioids are in that class; for example, morphine, hydromorphone, oxycodone, oxymorphone, buprenorphine, and even dextromethorphan and naloxone.

There are a number of different drugs that are in that pharmacological class, and it's really important to recognize, for example, that there are very different drugs that are in that class.

Page 115

Unfortunately, there are a number of people that I consider anti-opioid zealots that will tell you that, for example, OxyContin is synthetic heroin. I've seen it in the press. I've heard it on auto podcasts and things like that. It's simply not true. Dextromethorphan is in that class, and so is naloxone, which blocks opioids.

The chemistry is important. Dr. McPherson talked about the lack of therapeutic response or adverse effects. If you look over in the very last column --

DR. CHAI: Dr. Fudin?

DR. FUDIN: Yes?

DR. CHAI: I'm sorry to interrupt you. I think we're a little bit off on your slides. I'm sorry to interrupt. We can try to orient you back.

DR. FUDIN: Okay.

DR. CHAI: My apologies.

DR. FUDIN: Okay.

DR. CHAI: Chidi, are you able to get us back on track with the slides?

(Pause.)

Page 116

DR. CHAI: Well, it's a good thing we are ahead of schedule. We're just going to take a minute to try to get the slides back, because I think it's very important to be able to see the slides as you're walking us through.

DR. FUDIN: Yes, okay.

DR. CHAI: So please give us a minute.

DR. FUDIN: Sure.

DR. CHAI: Yes. Sorry about that.

DR. FUDIN: That's okay.

(Pause.)

DR. CHAI: It's been a very interesting year this year, but we're fortunate to be able to have this meeting, despite having it virtually.

(Pause.)

DR. FUDIN: Great. Okay. It's looks like we're set, right?

DR. CHAI: Yes. Thank you. Please go ahead.

DR. FUDIN: We're on the slide of the chemistry. As I was saying, the first column is the majority of most commonly prescribed opioids.

Page 117

In that column, we see things like buprenorphine, naloxone, which obviously is an opioid blocker, and naltrexone, the same thing; and also dextromethorphan, over-the-counter cough syrup. But we also see things like morphine, oxycodone, and oxymorphone.

Now, I started to mention that Dr. McPherson was talking about lack of therapeutic response. If you hop over to the third column, you'll see, for example, methadone. Now, methadone, which is a diphenylheptane, is a drug that not only has opioid activity but also blocks NMDA and blocks reuptake of norepinephrine and serotonin, which makes it particularly useful for neuropathic pain, probably more so than other opioids.

What if you put a patient on methadone, though, they tolerated oxycodone before, but it didn't work? So you switch them to methadone, and the methadone worked, but they were sick to their stomach and had hallucinations.

Well, it would be good then to put them back on a phenanthrene type opioid, in the first column,

Page 118

that had similar properties to methadone in terms of blocking NMDA, having opioid activity, and blocking reuptake of norepinephrine. And there is such a drug, and it's called levorphanol. So it's not just about switching one drug to another; it's also about the therapeutics.

The other thing I want to point out is the third column over where we have the phenylpiperidines. There you have fentanyl, for example, and all the fentanyl derivatives. But you also have illicit fentanyl. Unfortunately, I've seen practices that have stopped prescribing fentanyl because they think that all the reports of fentanyl deaths are the same thing as pharmaceutical fentanyl. They are not. The fentanyl found on the street is very different, sometimes more potent than fentanyl and sometimes less potent.

What are some of the general issues that we see with morphine equivalent daily doses, MEq's, or whatever you want to call it, and opioid conversions? Well first, there's a pharmacogenetic

Page 119

variability among patients. Not every patient is the same. We have to worry about drug interactions. We have to worry about lack of universal morphine equivalents, which Dr. McPherson nicely delineated for you, and also specific opioids that should never have a morphine equivalent daily dose.

Those include:

Methadone, because it has multiple mechanisms of action. Again, it's an opioid, a full-agonist opioid. It blocks reuptake of norepinephrine and it blocks reuptake of serotonin, which has no effect on pain, and it also blocks NMDA receptors, which are found in nerves.

Buprenorphine. Buprenorphine is a partial agonist and also an antagonist to kappa receptors, but it has a very high affinity for the opioid receptor, higher than morphine. And I'm going to come to that on a couple of slides from now.

Then tapentadol. Tapentadol is a full-agonist opioid, but it blocks reuptake of norepinephrine. It has about 18 times less than

Page 120

binding affinity to the morphine receptor compared to morphine.

Then there's tramadol. Now, some people think that tapentadol is a glorified tramadol, and that couldn't be further from the truth. Tramadol has no activity until it's converted from its parent compound tramadol to o-desmethyltramadol by the cytochrome 2D6 enzyme in the liver. It has 5 metabolites and heavily relies on the CYP system in the liver to metabolize it, whereas tapentadol does not require phase 1 metabolism at all, so there's less drug interactions.

I mentioned to you that tapentadol was 18 times less the binding affinity to the mu receptor compared to morphine. Tramadol is 6,000 times less. So yes, they have the same chemical nucleus but, no, they are not the same drug. They are very, very, very different. And anybody who thinks that tramadol could be a substitute for a full-agonist opioid needs to do some studying.

This next slide, conceptual dose-response

Page 121

curves of three different opioids, what I did in this slide -- it's referenced down the bottom for you -- is I intended to point out to you that if you give a full-agonist opioid like methadone, morphine, tapentadol, oxycodone, oxymorphone, whatever it happens to be, the more you give, the more activity you get, and the more toxicity you get.

If you give a partial agonist like buprenorphine, there's a plateau effect not only in the analgesic efficacy, but also in the toxicity, at least to some extent. For example, you won't continue to get CO2 accumulation as the buprenorphine dose goes up, but that will happen with full-agonist opioids. Then, of course, if you give an antagonist like naloxone or naltrexone, you get no effect on respiratory response. So that's sort of an easy way to compare some of these drugs.

This slide I title, A Rose By Any Other Name. We have different acronyms that we use for these morphine equivalents. We have morphine equivalent daily dose; we have DDD, defined daily

Page 122

dose; OMEQ, oral morphine equivalent dose; and MEDD, morphine equivalent daily dose.

They essentially all mean the same thing. But maybe, just maybe, what we need is not so much -- let me see if it's on this slide or not. Maybe what we need is a morphine analgesic equivalent, if that's even possible, or a morphine toxic equivalent. And, really, the only way to do that, because of patient variability, would really be to be measuring O2 levels, or CO2 levels, in the patient.

So it's really an impossible task unless we start using smartphones and technology in order to monitor these patients. It's not just a simple matter of math because not every opioid is the same and not every person is the same.

Here in the next slide we talk about mu receptor binding affinity versus the partition coefficient. The partition coefficient really refers to the concentration ratio of the un-ionized compound, which is different from a distribution coefficient, which on this chart, distribution

Page 123

coefficient refers to the concentration ratio of all the species of the compound -- let's say it's morphine -- whether it's ionized or not ionized.

The purpose of this slide, without getting into too much math, is to point out -- look on the top. Sufentanil has the smallest K value. The lower the K value, the higher the binding affinity to the mu receptor in the central nervous system. Sufentanil has a very, very high binding affinity to that mu receptor.

Look at buprenorphine, which is a partial agonist, and of course not only used for pain management but for opioid-use disorder. It has a similar binding affinity. In fact, its binding affinity to a mu receptor is higher than all the drugs below it.

Then if we look at, for example, morphine and fentanyl, we all know that fentanyl is a very potent opioid, but if we look at morphine and fentanyl that are highlighted there for you, they have a similar binding affinity to the receptor once they get to the receptor. That's very

Page 124

important; once they get to the receptor. They have to get there.

The next column is the partition coefficient. The partition coefficient, again, is the concentration ratio of an un-ionized compound. You see that fentanyl has a very high partition coefficient, and in this case, the higher the number, the more easily the drug gets into the CNS.

Look at buprenorphine. It has a higher partition coefficient than sufentanil, and as we go down, you see these various other ones. Morphine is actually pretty low, but fentanyl has a partition coefficient somewhere between sufentanil and buprenorphine.

So again, to think that we can do a simple equation of morphine to another opioid is just wrong. It has to do with the binding affinity to the receptor and how quickly the drug gets into the CNS.

Molecular weight is not quite as important in discussion here, but it's included in this chart. Then the last column, equivalent

Page 125

equianalgesic IM dose, now we're not talking oral to oral, but we're talking injectable. You can see there that sufentanil is up to a thousand times more potent than morphine, and buprenorphine is 40 times more potent than morphine. In fact, there are some studies that show as an analgesic, buprenorphine sometimes acts as a full agonist in terms of analgesia. This is just to point out that complexity, from a physicochemical standpoint, are some of the disparities.

This next article which I've posted, and is open access, I include so you can pull this out as a reference because this really outlines a lot of what is to follow in this lecture in terms of the disparities in trying to calculate these doses.

This next slide, which is Variability in Opioid Equivalence Survey, this is a slide that Dr. McPherson actually showed you kind of in a different way. It's a study that we did together. We did, as she pointed out, 319 respondents. We surveyed pharmacies, MDs, DOs, NPs, and PAs, and we asked them to convert from these five different

Page 126

drugs at fixed doses and tell us what they thought the equivalent was, the equivalent morphine dose was.

Unfortunately, it was difficult to swallow. As Dr. McPherson pointed out, for fentanyl alone, you have plus or minus 115 morphine milligram equivalents. That's pretty bad. Right? That is higher than a lot of the states have as a morphine equivalent cutoff of 90, and sometimes less.

If you look over at methadone, we have 111 plus or minus, so that's 222. Right? And you look, and 186 -- and I separate this by people that are trained in pain management, in palliative care, and none of the above. This is problematic because even if we make guidelines and we leave it to the clinicians, the clinicians do not all agree on what and opioid equivalent is.

This, actually Dr. McPherson also spoke a bit about this but in a different way, I think, than I'm going to speak about it. This is a study that we did looking at 8 different online opioid calculators. What we see here in the results is

Page 127

that we have quite a variability.

What we did when we did this study is we compared it to the American Pain Society tables that they had at the time when they were still a society, and we did that for all their conversions. Even if the conversion was not exact, we were comparing like to like, so it didn't really matter because we were using the same equation.

Again, patients were either underdosed by 55 percent or overdosed by 242 percent. And look at the two drugs there that had the highest risk. They are fentanyl and methadone. That's a problem; obviously, that's a problem. I showed you on the previous slide that fentanyl and methadone were outliers in terms of what people thought were their conversions. Now, whether they used the opioid conversion calculator or they did it in their head, I don't know. But the point is that fentanyl and methadone are particularly dangerous here.

Then there's this, the variation when we do opioid calculations converting morphine to methadone. Ripamonti back in 1998 I believe is the

Page 128

first one to publish any guidelines on this, and it was based on only 38 cancer patients, and basically said that if you're on between 30 and 90 milligrams of morphine, the conversion would be 3.7 to 1 to 1. That's the ratio. And if you're on 91 to 300, 7.75 to 1, and over 300, it's 12.25 to 1.

Ayonrinde came along in 2000 and said, well, if 3 points are good, then 6 points must be better, so he did the same type of thing and gave us these conversion ratios. Then Mercadante in 2001 published a paper, and if you compare Mercadante to Ripamonti, you'll see 3.7 was just rounded to 4; 7.75 was rounded to 8; and 12.25 was founded to 12.

None of these are accurate because the body doesn't say, oh, this person just took one more milligram than this last person, and therefore the body, we're going to flip a switch and the conversion is going to change.

What I did is I developed a formula, which I think just the math itself is kind of dangerous in doing conversions. Because of that, I held on to that until eventually Practical Pain Management

Page 129

developed a calculator, and I told them the only way I was going to help with this is that they use this equation for methadone, or did not even include methadone because, again, as Dr. McPherson pointed out, methadone conversions are not bidirectional. The more morphine you're on, the less methadone you need to replace it.

This basically shows you what these various different lines mean. This is kind of a scary thing. If you look at the different lines here, Ripamonti's is red. It's superimposable with Mercadante. That makes sense because it was like rounding 7.75 to 8, 12.25 to 12, so they're superimposable.

But look at Ayonrinde's, and that was the 6 data point one. In Ayonrinde's, that one data point that I circled, 300 milligrams of morphine equals 60 milligrams of methadone, but 302 milligrams of morphine equals 30 milligrams of methadone. So imagine if you did that bidirectionally what a disaster that could be. Then the formula that I created is that dotted

Page 130

line, and that kind of smoothes it out. I'm actually working with another group now to smooth that out even more.

This next slide is the CDC calculator methadone, and unfortunately if you look at the methadone here -- I circled it for you -- it's most consistent with Ayonrinde's formula. So that needs to be either taken out of the calculator, in my opinion, or it needs to be changed somehow. But it's pretty inaccurate because people use these conversions going both ways.

When converting opioids, there should be unanticipated risks of opioid-induced respiratory depression just for the reasons that I outlined so far, but there are many more.

Here's an example of fentanyl. They have the package insert. This is a 100-microgram patch. This shaded amount shows you the serum levels to expect with transdermal fentanyl. This is a problem.

To give you an example of a patient that I had, a patient was referred to me in his 80s, and

Page 131

he was on a 100-microgram patch for chronic low back pain and diabetic neuropathy. The doctor wanted to change the patient to oxycodone and he wanted and equivalent. I said, "I can't really give you an equivalent without doing a blood level." And he was like, "Well, can you guess?" I said, "I can't guess."

I would start the patient -- 82 years old, poor kidney function. The patient weighs, I don't know, 88 pounds or something like that. I said, "What we need to do is start this patient on oxycodone 2.5 milligrams 4 times a day, and then escalate it slowly. If you want, we reduce the fentanyl patch to 50."

Now, think about this. If we use a traditional opioid conversion, a 25-microgram patch is equivalent to 22 and a half to 60 some odd milligrams of oxycodone, so let's say 40 milligrams. So 40 milligrams times 4, we're talking about 160 milligrams of oxycodone would have been the conversion. And even if we reduce that by 50 percent, which the FDA I believe

Page 132

recommends, we still would have overdosed this patient.

So it turns out that the serum levels came back to be around let's say 3 nanograms per mL, which is -- no, actually it was even less than that. The patient had blood levels that were equivalent to a 12.5-microgram patch, which is 20 milligrams of oxycodone, so we cannot predict this, particularly in cachectic patients.

This next slide shows you the schematic for opioid metabolism. You can see on the top that codeine is converted to morphine by CYP2D6. Codeine has no analgesic activity in its parent compound form. It's a prodrug. Oxycodone has activity. It also gets metabolized, to a small extent, to hydromorphone, which is more potent, and then it gets metabolized by 3A4, its inactive metabolite, hydrocodone.

On the bottom, which I'd like you to really focus on and remember because I'm going to come back, oxycodone is metabolized by 2D6 to oxymorphone, and then oxymorphone is metabolized by

Page 133

3A4 to its inactive form, and oxycodone is also metabolized by 3A4 to its inactive form.

There are basically two bridges out. You think of getting out of New York City. There are only so many bridges out. So oxycodone, you get metabolized to its active form, which some people say oxymorphone is twice as potent as oxycodone -- maybe, maybe not -- but 3A4 metabolizes it to norooxycodone.

What would happen if those things were shut down or the bridges opened up, and it was very easy for them to convert? We're going to come back to that when we talk about pharmacogenetics.

Medication metabolism is important. Phase 1 metabolism involves the cytochrome or CYP. They're listed there for you, and the drugs on the right-top row are drugs that do require CYP metabolism.

For phase 2, they don't require CYP metabolism. They're easier to metabolize. You can see on the right side there that morphine, oxymorphone, hydromorphone, and tapentadol do not

Page 134

require CYP metabolism. We can also add levorphanol to that list.

Why is this important? It is extremely important because, as I told you on the last slide, oxycodone is metabolized -- and I'm going to go back -- by 2D6 to oxymorphone and 3A4 to norooxycodone, which is inactive. What if a patient was an ultra-rapid metabolizer of 2D6 and rapidly converted oxycodone to oxymorphone, which is more potent, and they were also a poor metabolizer of CYP3A4 -- I'm sorry, a rapid metabolizer -- no. Lets' say they're a poor metabolizer of CYP3A4, so they're getting activity from oxymorphone and oxycodone.

Now, what if the patient was an ultra-rapid 3A4 metabolizer, so they're rapidly metabolizing oxycodone to norooxycodone, which is inactive, and they're a poor 2D6 metabolizer? So they're not converting any oxycodone to oxymorphone. Basically, they will be able to tolerate a much higher dose of oxycodone because the active drug is not going to stay around long. Alright?

Page 135

Now, the patient, all of a sudden they're on OxyContin, or Xtampza, or whatever extended-release oxycodone they are, and then they have to change insurance companies, and the insurance company says, "I'm sorry. We don't cover extended-release oxycodone. You'll have to change the patient to extended-release morphine," and so you do that. Oh-oh. We have a big problem here because if you use the math to do it, you're not considering the patient's pharmacogenetics. Morphine does not rely on CYP metabolism. You will overdose that patient.

Now, if we go back and the opposite happens, that the patient's an ultra-rapid 2D6 metabolizer and they're a poor 3A4 metabolizer, then that's a situation where they would require a lower dose. In that case, if you change with the morphine, you're going to underdose them.

Summarizing on this next slide, genetic variability is important. Forty to 60 percent of patients do have this phenotype variability of being different kind of metabolizers. The most common CYP enzymes are listed there for you. Of

Page 136

those enzymes, 3A4 is the most common. This is not just for analgesics, but for all drugs that go to the CYP system, about 85 percent of them are CYP3A4.

So we cannot just do simple math. We have to think about pharmacokinetics. We have to think about pharmacodynamics and how the drug actually works. I gave you examples of certain drugs that have more of an effect, perhaps, on neuropathic radicular pain, things like tramadol, tapentadol, methadone, and levorphanol, and then of course pharmacogenetics.

So what does this CYP thing all mean? Just to make it clear for everybody here, because a lot of people throw around this term "CYP" or "cytochrome" and we're not really sure what it means, the first number is the identifying enzyme family, the letter is the subfamily, and the last number, believe it or not, is the order in which it was discovered; kind of crazy, but that's what it is.

What about drug interactions? Certain drugs

Page 137

can make the liver turn out more enzymes, more of those CYP enzymes. Those drugs are inducers. A great example of that is carbamazepine. It induces certain CYP enzymes.

Then there are other drugs that are inhibitors, things like erythromycin, clarithromycin. They inhibit 3A4. That would be quite dangerous in the patient on oxycodone. Then the drug that gets metabolized by the CYP enzyme is the substrate, and polymorphism is the genetic variability among a population, how different people have different enzymes. For example, in Japan, they have more 2D6 than Caucasians do, and as you travel around the globe, you can actually map out the enzymes and the populations change as you go around the globe.

How do we personalize these things and what are the other issues? This next slide talks about P-glycoprotein, and unfortunately, P-glycoprotein interactions are often not included in a lot of the pharmacy software packages. That's problematic.

I know I don't have time to go through all

Page 138

of these, but I'm going to give you an example, example number two, in a paper that our group published here up in Albany, where a patient was coming into the hospital and had endocarditis.

The patient was home on pretty good doses of oral morphine, but because of the endocarditis was also being treated with rifampin. Well, rifampin is a P-glycoprotein inducer. Morphine relies very heavily on P-glycoprotein to pull it back into the gut, so it's kind of a protective mechanism.

If the P-glycoprotein is elevated, then that means that less morphine is going to be absorbed. So imagine if this patient comes into the hospital and we're going to set them up for heart surgery and put them on IV morphine, they will be overdosed because IV morphine is not the same as PO morphine. PO morphine depends on P-glycoprotein. P-glycoprotein is a protective mechanism to pull drugs back into the gut so they don't get absorbed.

That's also an important consideration. A number of drugs either induce or inhibit P-glycoprotein, and also there are pharmacogenetic

Page 139

differences in P-glycoprotein amongst patients. P-glycoprotein also varies in the CNS and is important for carrying certain opioids across the blood-brain barrier.

What are the phenotypes? There's wild-wild, variant-wild, and wild-variant. You get an allele from the mother and from the father. If both have the wild gene, then you're considered a normal metabolizer, which is termed "extensive metabolizer." If you're a variant-wild or a wild-variant, so one parent is the variant and one has the wild gene and vice versa, then you could probably be an intermediate metabolizer. But if you're a variant and variant, then you're more likely to be an ultra-poor or ultra-rapid metabolizer.

This shows you what the difference is The first one shows if you're a poor metabolizer, you're not going to get as much metabolite, keeping in mind, again, that some of the metabolites are active and sometimes they're inactive. Intermediate metabolizer, you see a picture of

Page 140

that; extensive metabolizer, which would be normal, and ultra-rapid metabolizer. I'm showing you large M's and small M's for the different metabolites.

I'm going to go through a couple of cases really quickly to finish this up, and these are real cases.

JB is a 45-year-old Caucasian male who has a history of cervical stenosis at C5-C6 with myelopathy. He has been on tramadol for a number of years, but he comes to you for assistance with optimal control of neuropathic pain. You initiate carbamazepine 100 milligrams PO daily for 7 days, then 200 milligrams daily. Three weeks later, JB calls the clinic in distress. He reports being in the worst pain he has experienced in years.

Why is he suddenly in pain? He's in pain because it takes about 3 weeks for enzyme induction to happen. What happened is not only is tramadol a substrate for CYP3A4, carbamazepine induces 3A4, but carbamazepine is also an autoinducer. Not only does it increase CYP3A4 enzymes, but it itself is metabolized by 3A4. So not only did the tramadol

Page 141

levels go down in this patient, but so did the carbamazepine levels.

I think it's also extremely important to point out here that although induction, or having the liver put out more enzymes, takes 3 weeks, inhibition -- so a drug that inhibits an enzyme like erythromycin or clarithromycin -- only takes 48 hours, so that could be a disaster.

Here's a case, RC. The patient is a 48-year-old male with a past medical history significant for ADHD, OSA, PTSD, and chronic low back pain. The pain level on a visual analog scale of 0 to 10 was 9 out of 10. He was intolerant to many antidepressants: duloxetine, venlafaxine, citalopram, sertraline, bupropion, and mirtazapine. He had a mild response to morphine.

When we tested him pharmacogenetically, he had reduced activity for COMT. Now, that would actually, for neuropathic pain, be a good thing for him because COMT, catechol-o-methyl transferase, is an enzyme that breaks down the neuroamines of the synaptic space, so if he had reduced activity, he

Page 142

had more amines there. MTHFR, methylene-tetrahydrofolate reductase, reduced activity; 3A4-3A5 intermediate metabolizer, not usually too much of a problem; and the others were normal.

What about MTHFR? Well, MTHFR is important in treating depression. I don't care how many antidepressants you give to a patient, they are not going to work if you don't have the capability of converting folic acid to tetrahydrofolate acid. That's what MTHFR does. You need to have the active form.

So we treated this patient with L-methylfolate -- oh, no. You have a choice between L-methylfolate or leucovorin. The VA does not like using L-methylfolate because it's a natural substance, so I was forced to prescribe leucovorin or folinic acid. That, unfortunately, reduces zinc, so we supplemented the patient with zinc, and 8 months later this patient was stable, required absolutely no opioids at all, didn't need anything for ADHD, and was a changed person. We published this case study, and it's referenced

Page 143

number 2 for you.

Patient SR, 47-year-old female patient with 3 failed back surgeries; diabetic type 2; 5'6", weighs 200 pounds; medication regimen for the last 2 years, no changes; urine screen is good, no problems; 30 milligrams oxycodone continuous release every 12 hours; oxycodone IR 10 milligrams q4h PRN, usually took 2 or 3 a day.

Do you think that this patient is an elevated risk? Most people say low-to-moderate risk, and that I think on the face is probably true. Patient's tolerance to these opioids, doing well, being closely monitored.

But here's what we don't know. Medications prescribed by a psychiatrist include lorazepam every 8 hours for anxiety. Thankfully now, PDMPs are shared amongst most states. But what if the patient is placed on pregabalin 75 PO TID by the endocrinologist for diabetic peripheral neuropathy?

Then the patient decides to go on a grapefruit diet, which inhibits CYP3A4, and unbeknownst to us, the patient's an ultra-rapid 2D6

Page 144

metabolizer and they're converting oxycodone to oxymorphone. How do we know that if we didn't do a genetics test?

Patient develops an upper respiratory tract infection, which in and of itself is a problem, and then the patient decides to go to the pharmacy and pick up some Benylin cough syrup, which is Benadryl or diphenhydramine. We have a problem. Now the patient goes from low-to-moderate risk to a very, very high risk.

This is my last wrap-up slide here, Transforming Negative Perception in a Perfect World. There are problems, as was pointed out in the first couple of lectures this morning. What opioids are really killing our community and how? We need to be very cognizant of the fact that fentanyl is not the same as these fentalogues, or these fentanyl analogues, on the street. And I think that it behooves all of us, whether it's the regulatory agencies or responsible reporting in mainstream media, that pharmaceutical fentanyl is not the same as these fentanyl analogues on the

Page 145

street.
Secondly, community and patients, we need to educate and seek education from medical providers and from pharmacists. We need, I think, to support pharmacy provider status. I've heard several times this morning already that practitioners don't have enough time to see these patients. They had all the education to see these patients, to have the wherewithal to make some of the decisions that are required to be made, that will be made maybe in a specialty clinic.
There are pharmacists who are two years post doctorate, do pain and palliative care residencies, and who are stars in this area. Pharmacists can prescribe nationwide in almost all states in collaboration with physicians, but they are not paid by insurance carriers to see patients, and they could really help to mitigate these risks. But for some God unknown reason, Congress has not seen fit to make pharmacists providers, as pretty much all other clinicians that see patients are considered providers and are paid for it, but

Page 146

pharmacists are not.
So in closing, I'd like to ask everybody here to support provider status for pharmacists, and that is my presentation. Thank you very much for inviting me. Thank you to Grace and the whole team.
DR. CHAI: Thank you, Dr. Fudin. That was a very complex presentation, and it's really building upon the science that we are trying to share here at this workshop, and thank you for getting us back on track.
We will now hear from three speakers from the Veterans Health Administration, Dr. Friedhelm, Dr. Emmendorfer, and Dr. Cunningham.
Please take it away. Thank you.
Presentation
Friedhelm Sandbrink and Thomas Emmendorfer
DR. SANDBRINK: Good morning. I'm going to get started. I'm Friedhelm Sandbrink, and thank you, Dr. Chai and the FDA, for organizing this meeting and giving us the opportunity to talk about Opioid Prescribing and the Opioid Safety Initiative

Page 147

in the Veterans Health Administration.
These are our standard disclosures. Obviously, these are our personal opinions and do not reflect the official views of the Department of the Veterans Affairs or any federal agencies.
I will get started with an overview about pain management and opioid safety in veterans receiving care in the VHA, and then together with Dr. Emmendorfer, we will talk about the Opioid Safety Initiative specifically, and opioid prescribing, and opioid risk mitigation. The third section will be by Dr. Cunningham about a deprescribing and tapering assessment that we did among veterans who discontinued opioid as part of a medication-use evaluation.
As a background, out of the 20 million veterans who we see and who are in the United States, about 9.7 million have contact, whether it's benefits or healthcare, with the VA, and about 6 million really receive health care, including primary care.
When we look at the assessment of what is

Page 148

the prevalence of pain in veterans in the United States, in general -- and this is not all of United States -- I'm showing here the data from the National Health Interview Survey in 2016 that specifically talked about the subset of patients who have severe pain, and that's 9.1 percent in veterans that was 40 percent more common than the non- veteran population.
These are mostly musculoskeletal pain conditions. But if you look at this over on the right side -- this is stratification according to age -- you will see that blue are the columns for the prevalence in veterans. And even at a younger age, really across the board, the number of veterans who have high-impact pain, have severe pain, is significant, and it centers around the 8 to 10 percent range.
When we look at the 6 million veterans in the VA who receive their care within primary care, 2 million have a pain diagnosis, but it's only 120,000 in this analysis from 2012 that get seen in the pain clinic. So when we make guidance for pain

Page 149

management, we always have to keep the primary care in mind and the general care that we provide.

Again, this analysis, also about internal VA veterans, shows that 1 in 10 had severe persistent pain. But this analysis of those patients who had severe pain who attended the pain clinic shows that mental health conditions really is what separates those patients who have severe and persistent pain.

This is in regard to our overall prescribing and implementation of multimodal pain care. This is a study that only goes to 2015, but as you can see here, on the right side in the graph in the violet-purple and the light green, that is opioid prescribing, and specifically in the light green is the long-term opioid therapy.

Those numbers have been trending down steadily since 2010 already, whereas others, which here is access to physical therapy and opioid therapy and behavioral health care, have significantly increased.

When we look at the risk, though, of veterans in the Veterans Health Administration in

Page 150

regard to opioid overdose and in regard to suicides, we know from our epidemiological data that the mortality rate for opioid overdose is about 1.5 times greater in VHA veterans than in the general U.S. population. This analysis here looked at 2016 data where there were 1,271 deaths of VHA veterans from an opioid overdose. That's about 3 to 4 veterans a day.

We also realize that the suicide rate is about 1.5 times greater in VHA veterans than in the general U.S. population. We note that pain is the most common factor among veterans who die by suicide, and we heard this also from Penney Cowan earlier today, that opioid prescribing, and especially deprescribing, and opioid discontinuations, abrupt discontinuations, are at least anecdotally reported to be connected with suicide risk or suicide attempts.

The bottom line, though, is that we have to integrate the mental health assessment and the treatment of mental health factors into our pain care.

Page 151

There are other studies obviously not just for veterans, but we have several studies looking at the risk of opioid overdose correlated to the opioid dosage and morphine milligram equivalent and MMEs.

This is Dr. Bohner's study here in blue that shows obviously that the higher the dosage is, the higher the risk is for an unintentional overdose. The increase with dosage in regard to risk of suicide is also there, but the factor is certainly smaller. It's about a factor of 2 times for suicide risk at 100 milligrams or higher of morphine equivalent versus a factor of 7 times higher in this study for unintentional overdose.

We do have to realize that these are correlations that are being noted, but it doesn't mean that that's the opioid prescribing in itself. It may be the mental health factors that lead to severe pain and opioid prescribing in itself that actually drives suicide risk.

We did an analysis recently looking at data from 2013, looking at every patient in the VA

Page 152

system who was on opioid medication, and followed them up to the end of 2014 in regard to what were the factors and what were the characteristics of those patients who had a mortality from an overdose or from suicide.

This is comprehensive observational data that we did in the VA system, but as you can see here, the dosage, the most common dosage of patients who die of an overdose or suicide is in the lower dosage range. It's 20 to 50 milligrams morphine equivalent because the vast majority of patients who are on opioid medication long term are on these kinds of dosages.

If you just concentrated on the high-dose opioid therapy patients, if I take the definition of more than 90 milligrams of MME, that would capture only about 20 percent of all patients who in 2013 were on such a dosage or on an opioid medication and then had a death from a suicide or an overdose by the end of 2014.

Four out of 5 patients had dosages below the 90 milligrams of morphine equivalent; 3 out of

Page 153

4 opioid overdose patients or suicide deaths were among patients who had a mental health or substance abuse diagnosis; and in red here are the mental health diagnoses; other; then blue is the SUD diagnosis.

So with this, I'm going to lead over now towards our Opioid Safety Initiative in the VA system. That was piloted in 2012 and then expanded nationally in 2015. Clearly, the Opioid Safety Initiative aim included, obviously, a reduction of the overreliance on opioid analgesic medication for pain management when it may not actually be needed, and at the same time to make opioid prescribing and opioid therapy more safe and also more effective than actually clinically indicated.

We developed an OSI dashboard. PBM developed that together with other stakeholders to make the total opioid prescribing visible within the VA system. But we also realized very early on that what we needed was a comprehensive strategy, like an opioid stewardship initiative across the VA system that also takes in provider education and

Page 154

broadens access to non-pharmacological modalities, because the goal is, of course, better pain care and better improvement in regard to the management of pain, and better function of our veterans.

So we had to make sure to include and expand the access in regard to behavioral and CIH modalities, as well as physical therapy modalities and other restorative and interventional providers. Specifically, we included the development of an academic detailing service within the VA system for provider education but also for patient education.

I'm just going to show you two slides about our VA/DoD Clinical Practice Guideline for opioid therapy that was published in 2017; clearly, a very important component of our Opioid Safety Initiative. It does have 18 recommendations. Many of them are very much aligned to the CDC recommendations established shortly before the VA/DoD Clinical Practice Guideline, but there are a few nuances, just a few differences.

One, obviously, is that we actually made a recommendation against -- and this is here that I

Page 155

want to emphasize -- initiation of long-term opioid therapy. We didn't say make a recommendation against patients on long-term opioid therapy already on there. We also didn't say that you shouldn't prescribe opioids when they're clinically indicated in particulars such as for short-term use. But we felt that there were really data out there that suggested that a general recommendation against initiation of long-term opioid therapy as a guidance, the guideline document was appropriate.

The second component that we did in this clinical practice guideline is that we said that opioid dosage reductions must be individualized to the patient. We specifically issued caution against sudden reductions; indicated that opioid tapering, if it is being pursued for risk greater than benefit, has to be done very slowly.

(Background noise.)

DR. SANDBRINK: If everybody can mute their phone.

DR. CHAI: We'll pause here.

Could everyone please mute their phone?

Page 156

DR. SANDBRINK: Thank you.

DR. CHAI: Thank you.

DR. SANDBRINK: So we did make caution against sudden or fast discontinuations of opioid medication, and obviously included risk about opioid-use disorder and the availability of access to treatment for patients who may be affected by that.

So with this, I will hand it over to Dr. Emmendorfer, who will tell you more about our Opioid Safety Initiative and risk mitigation factors that we've been implementing.

Tom, can you take over?

(No response.)

DR. CHAI: Dr. Emmendorfer, should we try to pull you up on audio? Are you able to hear us? Can you chat?

DR. SANDBRINK: So while we're waiting for Dr. Emmendorfer to come on, I can maybe get started with presenting the first part of his slides. And, Tom, whenever you're on let us know, and you can take this over.

Page 157

DR. CHAI: Thank you, Friedhelm.
DR. SANDBRINK: Oh, wonderful.
(Pause.)
DR. CHAI: Would you like to try to present a few of the slides for Dr. Emmendorfer until we're able to get him on?
DR. SANDBRINK: Yes, I'd be happy to do that.
DR. CHAI: Okay. Thank you.
DR. SANDBRINK: Alright. I already mentioned that we have this Opioid Safety Initiative dashboard that we established to make the opioid prescribing visible across the system.
DR. EMMENDORFER: Can everybody hear me now? I just disconnected from the phone and tried through the laptop.
DR. SANDBRINK: Yes, we can hear you now.
Tom, please, go ahead. Tom, we can hear you.
(Pause.)
DR. SANDBRINK: Could hear you.
(Pause.)

Page 158

DR. SANDBRINK: Alright. Tom, let us know when you are on.
The Opioid Safety Initiative dashboard included information -- and it does and continues to include -- about total opioid prescribing, specifically about opioid and benzodiazepine co-prescribing, and then the high-dose opioid prescribing.
In the past, we defined it as greater than 100 milligrams of MME. Now we are defining, and we have adopted the more general standard of 90 milligrams of morphine equivalent, and we've back-calculated our dashboard accordingly.
We also will show you data about long-term opioid prescribing and implementation of risk mitigation strategies, in particular urine drug screens, and the other parameters that are listed here. We will show you some of the information about these parameters. They include, obviously, an informed consent.
Tom, are you on?
DR. EMMENDORFER: I'm on, Friedhelm.

Page 159

I apologize to everybody. I was on the phone, and I was already halfway through the slides, so I apologize for that.
Thank you, Dr. Sandbrink.
DR. SANDBRINK: Alright.
Presentation - Thomas Emmendorfer
DR. EMMENDORFER: When I was rejoining, I missed what Dr. Sandbrink said about the slides, but the bottom line is I believe he's probably went over the dashboard metrics.
None of these metrics had any target measurement goals, and that was done on purpose. All of the metrics have been recalibrated in fiscal year '21, so just recently, to align with the Centers for Disease Control definitions because the VA Opioid Safety Initiative was launched in 2013 prior to some of the definitions being available.
I heard Dr. Sandbrink talking already about our other risk mitigation strategies. And if you didn't make it to the OSI risk review based on STORM, I just want to highlight that's a good example of the multidisciplinary approach that VA

Page 160

has between all of our different national program offices. Really, mental health had the lead on this, and Dr. Sandbrink's earlier slides mentioned the importance and the role that mental health plays in the overall clinical picture of our veterans that we care for.
Just to quickly orient to the slides, these next four slides, the top graph is the veterans dispensed opioids over time, and it will always be a number value, and the bottom graph expresses that as a percent.
The bottom graph, the blue color line is the percentage of VA patients from a VA provider. We've always historically used community care providers in VA as well, so authorized community care providers, and that percentage is in red on all these metrics.
For the purpose of time, I'm not going to spend a lot of time on these slides other than I want to point out that you're going to see a very similar trend in all of our enterprise metrics that can be aggregated at the facility, or the regional,

Page 161

or our national at the enterprise level.
You'll see at an enterprise level, VA has been trending from quarter 4, fiscal year '12, which for us ends in September for that quarter 4 period, and all the way through quarter 2, fiscal year '21, which ends in March of '21. So that's the time frame for all of these slides.
The big changes for harmonization purposes with the Centers for Disease Control is the morphine equivalent daily dose. Back in 2013, before CDC came out with their guidance, we had established greater than or equal to 100 morphine equivalent daily dose, and we have harmonized that with the CDC. Really, the other big change is this metric here, where our original metric we did not include tramadol, and now we do for veterans dispensed opioids over time.
The veterans dispensed opioid and benzodiazepine, the similar trend, veterans on high-dose opioid therapy, which we define as greater than or equal to 90 morphine equivalent daily dose per day. This sets up nicely

Page 162

Dr. Cunningham's presentation here in just a minute that's going to discuss the findings of the medication use evaluation that was conducted to assess patient characteristics and patterns of the deprescribing or tapering of chronic high-dose opioids.
This one shows the veterans on opioid long-term therapy over time and seeing the similar trend, and then veterans on opioid therapy receiving a urine drug screen in the last 365 days. You'll notice that it did drop a little bit, and that also does have some correlation potentially with COVID-19.
This is our newest metric which shows veterans with new long-term opioid therapy in our system, and you'll see that that is showing the same trend over time.
The one risk mitigation strategy that we did want to spend a little bit of time talking about is our overdose education and naloxone distribution program. The take-home point here, this program is really ensuring that the education piece is just as

Page 163

important as the naloxone distribution piece.
VA has really done a phenomenal job of implementing this program, and it's no cost to our veterans, so there's no prescription co-pay for the naloxone, and we've removed every barrier we can in our healthcare system. We've been funding the naloxone centrally so it does not come out of the local facilities' budget. As a result of that, the most updated numbers that we have go through March of 2021. We've had over 500,000 prescriptions dispensed, and we've had greater than 1800 overdose reversals documented in our electronic health record.
This next slide shows the trends over time. Probably the most important one here is on the right, which shows our at-risk veterans dispensed outpatient naloxone, looking at both those veterans based on morphine equivalent daily dose as well as the opioid and benzodiazepine veterans. So over time, those percentages are going up significantly in our healthcare system.
DR. SANDBRINK: Thank you, Tom.

Page 164

DR. EMMENDORFER: Yes. Sorry.
DR. SANDBRINK: One of the other opioid risk mitigation strategies, or really for all controlled substances, is the prescription drug monitoring programs. This highlights that we have just recently, at the end of the last calendar year, implemented the system, a technical solution for our providers that will allow the PDMP queries within the electronic health record. So it's really readily available to obtain that information for more participating states.
We have four states that don't participate yet, so providers cannot use this integrated solution to see their data. But all the other states and PDMP systems are on board, and hopefully we can get all the states on this in the near future.
I have two slides here that are about our approach for opioid tapering. I'm not going to belabor this. The bottom line really is, as I said earlier, that we cautioned against involuntary tapers. We really educated our providers about the

Page 165

concerns that patients have and may have, and we got opioid dosage reduction, encouraging discussions and a conversation about what the goals of treatment are, taking any concerns into consideration and having patient-centered decision making in regard to the next steps.

In 2016 and '17, or 2016 already, we did recommend that if a provider and the patient are pursuing an opioid dosage reduction that, in general, the reduction should be very slow. We mentioned 5 to 20 percent every 4 weeks at that time as a suggestion, so it's about 10 percent a month.

Realizing that there was no clear data in the literature to suggest a specific number, we did not put a specific number as a recommendation into our clinical practice guideline, but taking these concerns into account, we've streamlined our opioid taper decision support tool for our providers accordingly.

I want to mention this tool that we developed in the VA system. It's called the

Page 166

Stratification Tool for Opioid Risk Mitigation. STORM is how it's commonly known. It takes individual patient factors into account to really develop a predictive analytic estimate of what the risk is for an overdose or suicide in the next year and in the next three years.

So it really gives you a score, a risk score, that is based on the patient's individualized factors and allows really meaningful discussions with the patient about what the concerns are. But also the STORM dashboard highlights what risk mitigation strategies can be still implemented to make care possibly safer.

We've used STORM, this dashboard, now to establish at every VA facility a team, a STORM risk review team that takes these database risk reviews and makes recommendations for the care of those patients that are identified as very high risk.

Our first data clearly shows that this approach actually is saving lives, and we've made care for our veterans safer, and that providers take this guidance that they receive into account

Page 167

to make decisions with our patients and to support them.

There was one observational study that I briefly mentioned already. I just want to show the slide from this. It's an observational study that looked at those patients, from 2013 and looked at the probability of a death from that overdose or suicide, treated with this opioid in 2013, after stopping opioid medication, in correlation to how long patients had been on opioids before.

You can see these four lines here on the graph, and the dashed blue line, that's previously treated for more than 400 days. So really, on long-term opioid therapy, you can see that, in particular, the higher the dosage, the higher the risk after the opioid stoppage, after the last opioid prescription has happened for a death, of an outcome of a death.

The correlation, in particular in the first 25 days, is very high. We took this to guide our providers to truly mitigate risk if, out of whatever reason, opioid medication is being

Page 168

stopped, and for the next 3 months after starting or stopping opioid medication, that the support is intensified and there's ongoing communication and interaction with the patient.

Also, part of what we do in these opioid risk reviews is we look for patients who may have opioid-use disorder to make sure that we provide access to MOUD, medication opioid-use disorder. Specifically, pain clinics and primary care clinics are included in what we call level one, addiction-focused medical management that we integrate where patients and providers are.

We're realizing that patients may be at risk for being identified as having abnormalities or irregularities in regard to their opioid prescribing and when the opioid is discontinued, and there's clearly access integrated into all pain management teams to allow access to opioid-use disorder treatment if clinically indicated.

With that, I will hand it now to Dr. Cunningham to talk specifically about our medication use evaluation.

Page 169

Presentation – Francesca Cunningham
DR. CUNNINGHAM: Thank you so much, Dr. Sandbrink.
I'm going to go over, for the last portion of our presentation, our national medication use evaluation for the deprescribing and tapering among veterans who discontinued opioids. Just for a quick overview, for those that may not be aware of our healthcare system and how we conduct these, we conduct national medication use evaluations.
What does that mean? That means that we gather multiple sites from across the VA healthcare system so that we have geographic representation from each region of the VA healthcare system, and then can make some semblance of a national assessment or conclusion accordingly.
Now to that end, we develop these data collection tools and questions specifically addressing, in this instance, deprescribing and tapering. Then we ensure that this is done sequentially and also done the same way across the system by training reviewers, having multiple

Page 170

meetings, and also ensuring that all questions are asked and answered in a timely fashion so that this can be done relatively rapidly, and we can address and get specific information to make decisions.
Again, this is done from an operations standpoint. We get input from our collaborators, both throughout the VA and also stakeholders outside of the VA when needed. And for this particular project, we did obtain information or allow our stakeholders outside the VA to evaluate some of these questions that we were going to ask.
The objective was really looking at bullet point number 2. We conducted an MUE to assess patient characteristics and patterns of deprescribing and tapering chronic high-dose opioids among OSI veterans who discontinued opioids in either fiscal year '13, which was the initiation of the Opioid Safety Initiative, very early, versus fiscal year '17, which was later in the process for evaluating our Opioid Safety Initiative to assess changes in management and outcomes over time; and really to see if we were improving over time,

Page 171

keeping in mind that OSI was initiated in fiscal year 2013.
We have a sample of pertinent measures that we wanted to look at. We wanted to describe documented plans for tapering and deprescribing of high-dose chronic opioid therapy in our given cohort, so we assessed if there was a document-tapering plan, the reasons for discontinuation VA services that were responsible for recommending and implementing the discontinuation of an opioid, specifically looking at primary care independently, as well as what happened over time: primary care, pain specialty, pharmacy, and others that assisted in the deprescribing process.
We looked at the target MEDD prior to discontinuation and tapering versus no tapering. We looked at gradual versus quick taper and the length of tapering period.
I'm going to go through some results very briefly with you, some pertinent results. We looked at a lot of things, but I am going to only present to you those that are most important.

Page 172

Specifically, we looked at the characteristics. We were interested in the basic demographics, as well as other pertinent demographics for us, and level of completed education, as well as employment status to see if that influenced anything from our standpoint.
As you can see highlighted in red, the patients in fiscal year '17 were significantly older than those in fiscal year '13. Ironically, but also very good from an MEDD standpoint, if you looked at the MEDD standpoint --
DR. CHAI: Sorry, Dr. Cunningham. My apologies. We're going to have to ask everyone to refrain from touching the panels. It is changing the view for the entire audience. I think we're having some technical difficulties.
DR. CUNNINGHAM: Okay.
DR. CHAI: I'm sorry, Dr. Cunningham.
Let us try to get us back on track so that we can see your slides as you're talking through them.
DR. CUNNINGHAM: Okay.

Page 173

DR. CHAI: It seems that there are some people who are getting dropped, so hopefully they'll call back in.
DR. CUNNINGHAM: Okay. Do you want me to continue to advance, or no?
DR. CHAI: Can you see the slides on your end? Mine are blank.
DR. CUNNINGHAM: I can see the slides on my end, and I am looking at -- the title says, Baseline Demographics and Other Characteristics of Chronic Opioid Discontinuers.
DR. CHAI: Okay.
Let me just confirm with the AV staff real quick. I'm sorry. It's blank on my end, and then I'm getting notices that it's blank on many others' screen.
(Pause.)
DR. CHAI: I'm sorry, Dr. Cunningham. Thank you for your patience.
DR. CUNNINGHAM: That's ok. Maybe I can say "next slide" so that I don't touch the slides, too.
DR. CHAI: Yes. Unfortunately, it's blank

Page 174

for many of the audience. We may have to be flexible and take lunch early. I think we're just going to be flexible and just rearrange the agenda a bit.
DR. CUNNINGHAM: Okay.
DR. CHAI: Would you mind coming back in after lunch and finishing your presentation? And then we can go into clarifying -- oh, you can't?
DR. CUNNINGHAM: I can. I can. I may have to leave right --
DR. CHAI: Oh, you can.
DR. CUNNINGHAM: -- I can -– before the clarifying questions and then rejoin, because I have another commitment, but I can rejoin right after that. So I'll be able to finish for sure, and then I'll let you know.
DR. CHAI: Thank you. Okay, great.
Let me note the time. One second while I calculate the time.
(Pause.)
DR. CHAI: If we could have everyone return at 1 p.m., I think we can finish out your

Page 175

presentation, and then do quick clarifying questions before turning it over to CDC's presentation. Would that work for you, Dr. Cunningham; 1 o'clock?
DR. CUNNINGHAM: That definitely works. That works.
DR. CHAI: Please let us know if any of this is going to impede schedules. My apologies. We're just going to have to be a bit agile since Adobe Connect seems to have dropped many members of the audience, as well as panelists.
DR. CUNNINGHAM: It's ok.
DR. CHAI: I'd just like to adjourn everybody for the break for lunch. Please plan on returning back promptly at 1:00 p.m. For panelists and speakers, please ensure that you're able to get back in before 1 o'clock; if you can just check with the AV team that we are able to connect you again. Thank you everybody. See you back at 1.
DR. CUNNINGHAM: Thank you. Bye.
(Whereupon, at 12:19 p.m., a lunch recess was taken.)

Page 176

A F T E R N O O N S E S S I O N
(1:00 p.m.)
DR. CHAI: If you have joined us back for the 1 p.m. mark, please give us a few more minutes. We're just working out a few Logistics. Thank you.
(Pause.)
DR. CHAI: Dr. Cunningham, is your audio connected.
(No response.)
DR. CHAI: While we're waiting for Dr. Cunningham --
DR. CUNNINGHAM: I am on.
DR. CHAI: Oh. Thank you.
DR. CUNNINGHAM: Sorry. I just got on.
DR. CHAI: No. That's wonderful. Thank you for your flexibility and patience.
Just to orient everyone, thank you and welcome back from lunch. We've changed the agenda a bit, but we'll finish hearing from our VA presenters, and then move on to a clarifying questions session.
So we've reordered a bit to move lunch

Page 177

ahead, but we will be back on track shortly.
Thank you, Dr. Cunningham. Please take over.
DR. CUNNINGHAM: I am going to take over now and try to -- wait a minute. I do not see where I can push "next," where I was able to do that before.
DR. CHAI: Gideon, will you be advancing the slides for Dr. Cunningham?
AV TECH: We can if she'd like.
DR. CHAI: Okay.
Is that ok with you?
DR. CUNNINGHAM: Please. Yes. I would like to go back to the slide that I left off on, so please go down to next. Okay. We can stop right there. Thank you.
Thank you, everybody, for allowing me to continue, and I'm going to try to wrap this up as quickly as possible.
Going back to our results, we really wanted to focus on the specifics, primarily what changed between fiscal year '13 and fiscal year '17. We

Page 178

looked at a few different areas, primarily interested in seeing -- what slide is showing? I want to make sure I know what slide is showing to the audience.
DR. CHAI: Could you describe your view?
DR. CUNNINGHAM: Yes. My view is I'm seeing all slides. I'm seeing right now a graphic slide, and now I do see a table slide that states, Discontinuation: Clinician Involvement.
DR. CHAI: Okay. I see the same. Which slide number would you like us to go to? I see 5.
DR. CUNNINGHAM: Yes, if you could skip to slide 5, that would be perfect.
DR. CHAI: Okay. Thank you.
DR. CUNNINGHAM: Okay. No problem; no problem.
So just looking at slide number 5, we really wanted to focus on the differences on how the discontinuations changed between fiscal year '13 and fiscal year '17, primarily looking at, hopefully, an improvement between the different years.

Page 179

If you look at fiscal year '13, primary care with the primary provider that discontinued or worked with discontinuing and tapering, that changed in fiscal year '17, where there was more multidisciplinary approaches, specifically with pain management and with primary care.
If you look at the other items, specifically looking at the differences in the deprescribing patterns and the reasons for the deprescribing patterns, earlier on, the deprescribing patterns were primarily for over-use of a given opioid.
If you look at what happened in fiscal year '17, there were multifactorials, specifically where more emphasis was placed on the deprescribing in regards to the risk outweighing the benefits; also ensuring that the patients weren't on too high of a dose; and also ensuring that the functionality of the patient was taken into consideration when they discontinued, again improving with fiscal year '17 versus fiscal year '13.
One of the other items we wanted to look at, specifically with those patients where we were able

Page 180

to identify the tapering, is looking at the modes of tapering, modes of therapy and pain management after opioid discontinuation, fiscal year '13 versus fiscal year '17. The fiscal year '13 is on the left-hand side and fiscal year '17 on the right. The fiscal year '13 appears to be blue and the fiscal year '17 appears to be yellow. I'm looking at it here; hopefully that's the same colors you're seeing.
What we saw is that the non-opioid pharmacological treatment was greater with the fiscal year '17 versus fiscal year '13 of non-opioid pharmacological treatment. Although it wasn't significantly different, it was still greater.
If you look at the non-pharmacological treatment in fiscal year '17, it was improved over fiscal year '13, as well as those patients that received any kind of treatment. No treatment was higher in fiscal year '13 than it was in fiscal year '17.
So again, if you looked at the overall

Page 181

treatment plan and modes of therapy, it was better in fiscal year '17 than in fiscal year '13, and the pain improvement was also significantly better in fiscal year '17 than in fiscal year '13, and that's in the last box on the right-hand side.

One of the other items we wanted to look at is monitoring activities, so we wanted to see if there are changes or improvement that occurred over time. The risk versus benefit improved in fiscal year '17, 59 percent versus 47 percent. It was significantly different.

Then again, if you look at VA services during the tapering period, in fiscal year '13, behavioral sciences was greater than in fiscal year '17. But for the other pertinent areas, specifically pain management and pain clinic, CAM therapy and pharmacy consult, those were all greater in fiscal year '17 than in fiscal year '13, so that also began to improve over time.

We looked at the modes of therapy, and looking at that, I think I went over that briefly earlier when I showed you that the modes of therapy improved

Page 182

between fiscal year '17 and fiscal year '13, so overall, we had an improvement of therapy.

Our MUE showed that therapy definitely changed in regards to discontinuation and tapering methods. The MUE provided a comparison of opioid discontinuation and tapering methods and prescribing practices between the years of fiscal year '13 and '17.

Although primary care was the main discipline, over the years we saw a multidisciplinary approach. As was described in the other slide, this was measured in these when we did the direct comparison between fiscal year '13 and '17.

Specifically, the high-dose opioid tapering plans were significantly longer compared to fiscal year '13 and were dynamically customized to the patient responses, which was definitely improvement over time. The final median opioid MEDD was significantly lower in fiscal year '17 prior to discontinuation when compared to fiscal year '13, and the pain management and improvement was

Page 183

significantly better compared to fiscal year '13.

So all in all, we showed that our healthcare system was a learning healthcare system. We did see an improved response over time when we looked at the various responses in measurement between the two years.

I'd like to wrap this up by just giving you some key resources that were used that you can identify when you're looking for our website in VA for pain management; for substance-use disorder; for OEND; academic detailing services; and also other items such as the DoD/VA Joint Pain Education Program, all listed here.

Questions?

DR. CHAI: Thank you, Dr. Cunningham, and thank you for your patience and flexibility during our extraordinary circumstances. We're all learning and doing really well, so thank you for that.

DR. CUNNINGHAM: Okay. Thank you.

Clarifying Questions to Speakers

DR. CHAI: I appreciate a very comprehensive

Page 184

and insightful presentation from Dr. Sandbrink, Dr. Emmendorfer, and Dr. Cunningham. What we'll now do is our clarifying questions for the presentations you have heard today.

We have divided the clarifying questions up into blocks so that we can try to handle as many as we can within our 15 minutes. What we'll ask you now to do is to please raise your hand. Use the raised icon -- and this is for all panelists and speakers -- to indicate that you have a question, and to remember to clear the icon after you have asked your question.

When acknowledged, please remember to state your name before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

I understand there's been a lot of material

Page 185

covered, as well as many slides, so if you have a sense of which presentation and can describe the slide to some extent, we can try to find that for you. But what we ask is to please refrain from adjusting or moving the slide yourself because it will change the view for the entire audience. And with multiple people doing that at the same time, it will essentially become chaos. So what we're going to have is our AV team get us to any specific slide if we need to refer to it.

So now at this time, we'd like to open it up for clarifying questions. I think we can start with Dr. Fine.

Could you unmute your phone and state your name before you speak? Thank you.

DR. FINE: Yes. This is Perry Fine. Are you able to hear me satisfactorily?

DR. CHAI: Yes, very loud and clear.

DR. FINE: Oh, very, very good. This is for Drs. McPherson and Fudin, who both just did an extraordinary job at summarizing the complexities of the issues, as well as recent science and

Page 186

scientific development in the last, say, decade.

The question I have really dates back the last 10-15 years, looking at the Gammaitoni paper that Dr. McPherson cited, as well as a paper that was not cited but I think certainly deserves some acknowledgement. That is the Knotkova paper in 2009, published in the Journal of Pain and Symptom Management, from research at Memorial Sloan Kettering and others, that looked at all the variables with regards to clinical application of dose equivalency or analgesic equivalency.

At that point, it was pretty obvious that there was going to be no simple formula that was going to resolve all the clinical conundrums that had been raised.

So my question has to do with, really, the more practical issue of, given the scientific developments, it's really not the science that is driving morbidity and mortality, or clinical applicability, or effectiveness and so on. It's really the acceptance and the ability to think through, as these two have succinctly said.

Page 187

It's really more of not so much education, but getting people to do the right thing, to actually apply what is known about these variables and to use the clinical skills and judgment that, as Lynn said, we all went to school for.

Yet, I don't see that there's really much movement in the last ten years. And if we date back to the meeting we had at FDA in 2013, which would probably be useful to summarize at some point because that never really went very far, all the similar points were brought out, and yet eight years has gone by.

So I'm asking these individuals, and anybody else who wants to participate in the discussion, how do we practically move forward? It seems to be independent from science and more a social phenomenon. Thank you.

DR. McPHERSON: Well, Dr. Fudin, I can certainly take a crack at it. This is Lynn McPherson.

Thank you, Dr. Fine. That's a great question. I wish I had a great answer for you. Of

Page 188

course, anybody who teaches at a professional school is going to have this opinion about their content. I happen to think that every medical school, pharmacy, nursing, and also social work and chaplaincy, should have content on primary palliative care skills, which certainly includes primary pain management skills.

I think everyone should be -- I mean, everybody's going to die, and most people will have pain at some point in their life. So I think you have to start with education; what are the core minimum competencies, and then I think we have to hold these learners accountable in their experiential training as well so that it becomes incorporated into their practice. I mean, I'm not sure what else we can do. So those are my thoughts.

DR. FUDIN: This is Jeff Fudin. I agree with Lynn. And, Perry, you bring up some incredibly interesting points. As everybody here knows, there's no easy answer. But I think that beyond the education -- and I said this, really, on

Page 189

my last slide -- I think that pharmacists are just terribly underutilized. Some of the people here that are not analysts, patients, and the like, may not understand the education and role of pharmacists.

I think the government really needs to take a step to put pharmacists, really, in the limelight of what's going on here. We're talking about drugs. We're talking about pharmacogenetics, pharmacokinetics, and drug interactions. And there needs to be more collaboration not only between community pharmacists and their prescribers, but there needs to be more pharmacists in clinics, and they need to get paid for their work that they can and, in some instances, are already doing.

It's not that we don't have the knowledge. Most of the people that are prescribing don't have extensive knowledge, but I think that globally as a medical society, including all healthcare providers, I think that pharmacists are often overlooked as part of that team, and they have a whole lot to offer, not only in a clinic setting

Page 190

and a community setting, but also in a hospital setting.

I had a legal case where a patient was in the hospital on a stable dose of methadone for years, and he died in the hospital, and the presumption was that he was overdosed by giving a small dose of hydrocodone.

What really happened is he had an infection. He was given moxifloxacin, which affects the QT interval, and he had an elevated QT interval for methadone. And as I mentioned in my lecture, it only takes 48 hours for that induction inhibition, and the guy died.

So to me, I think it's really, really important -- and not for my own personal reasons -- that the government, all the agencies -- HHS, FDA, CDC, DEA -- really look at incorporating pharmacists more into direct patient care as a norm; not as an afterthought, which unfortunately it often times is.

DR. CHAI: Thank you, Dr. Fudin.

Just to orient everyone to this session,

Page 191

we'd like to keep it to clarifying questions, if possible. We are veering a bit into discussions that we hope to have tomorrow, so please keep your questions to clarifying questions, if possible. And please use the raised-hand icon, and I will call upon you to help organize this session.

Dr. Bettinger, could you state your question, please?

DR. BETTINGER: Yes. Hopefully this is a clarifying question. Hopefully, everyone can hear me ok here.

This question is actually also directed more towards Dr. McPherson and Dr. Fudin, based around how to convert between different opioids. Both of you went over a lot of various scenarios of how to convert.

I was just wondering -- and it could be helpful for especially all those listening today -- in particular for patients with chronic non-cancer pain who don't necessarily have access to really close monitoring, such as Dr. McPherson was talking about, palliative hospice care settings

Page 192

where nurses are integral every day or most days, what's the difference or what are some -- if you guys could clarify maybe between you -- specific recommendations that may differ in terms of the approach?

After you calculate the opioid to convert to, what could be some of the approaches to get the patient to that conversion; again, thinking from a chronic non-cancer pain setting? Thank you.

DR. FUDIN: This is Jeffrey, so I'll grab this one first.

I think that, actually, consistent with some papers that both Dr. Perry fine did with Lynn Webster, I think that we should not be stopping the medications immediately, and it's because we cannot predict the equivalence exactly.

So what I would do, I would begin to taper the drug that the patient is already on, maybe by even 50 percent, and then slowly introduce the new medication in an immediate-release dosage form slowly on a PRN basis, so that we can figure out what the tolerability is and what the needs are of

Page 193

that patient. Then it's going to be a matter of decreasing the original drug while slowly increasing the new drug.

If the patient is on two medications, let's say extended-release morphine and let's say immediate-release hydrocodone, for example, what I would do there is I might cut the MS Contin dose in half, and I might start to escalate the hydrocodone dose if my intent was just to put the patient on hydrocodone.

But if my intent was to put the patient on a fentanyl patch, well, then what I would probably do is reduce significantly the morphine dose. I would probably, again, use the hydrocodone for breakthrough pain. And when I got to a point that I felt safe, I would convert over to the fentanyl patch, and I would calculate it and then reduce it probably by 50 percent and use something for PRN.

Hydrocodone would be a good choice because the patient was on that, or immediate-release morphine would be a good choice because the patient was already on morphine. But the point is do it

Page 194

slow and do it gradual.

DR. CHAI: Thank you, Dr. Fudin.

DR. McPHERSON: If I could just add to that, I'm not as big of a fan of cross-tapering opioids because people tend to mess it up or they all of a sudden believe that they're a freelance pharmacist who can do this on their own, unless it's a crazy-crazy high dose of opioid you're converting from.

But I would rather go with my golden rule, which is be very conservative with the standing schedule dose. And at least for the purposes of titration, even in a chronic non-cancer pain patient, to explain, and I think educating the patient that this is a partnership.

I don't have a magic bean to say exactly where we're going to end up with this, so I need you to work with me on this. We're going to be liberal with the breakthrough for the next week until you can come back to clinic or whatever, so I need you to keep a good record for me, a medication administration record. I sometimes would even call

Page 195

the patient every day. You don't have to have a nurse go out, but I could call every day or every other day.

So be conservative with the standing. I agree with Jeff about cutting back up to 50 percent as you're doing a conversion, and be, especially in the beginning, a little more liberal with the breakthrough, and still keep a close eye on them. That's all I have. Thank you.

DR. CHAI: Thank you Dr. McPherson.

What we'll have to do at this time to keep up with the schedule is to transition over to Dr. Zhang's presentation. I'm sorry for the abrupt transition, but it appears that we don't have any outstanding raised hands at this point.

So thank you, Dr. McPherson and Dr. Fudin, for your responses to these questions.

Dr. Zhang, are you ready to give your presentation?

DR. ZHANG: Yes, I am. Can you hear me?

DR. CHAI: Yes. Thank you.

DR. ZHANG: Well, thank you so much.

Page 196

Presentation – Kun Zhang

DR. ZHANG: Good afternoon. I hope everybody got recharged during their lunch break because what a great morning we had. I think all the presentations, including the opening remarks, are just excellent, as well as the discussion we just had. I really want to thank the team at FDA for organizing this important meeting and inviting us to present.

My name is Kun Zhang. I am a health scientist and health services researcher with the Division of Overdose Prevention at CDC. It's a special great pleasure for me to present you an Overview of the Opioid NDC and MME Analytical File Compiled by CDC. I think my presentation is switching the gear a little bit from patient care to a more retrospective context. It's more about data and analytics.

Here is my agenda. I will first give an introduction of the opioid NDC and MME analytical file, which I will just simply refer to as the analytical file hereafter, followed by the purpose

Page 197

of the file and how the file was developed and compiled. Then I will show you how to use the file by looking at some real-world prescription and dispensing data together, as well as some specific examples from published studies or web applications.

Lastly, I will go over some important distinctions between the analytical file and the table of MME conversion factors, published together with the CDC guideline for prescribing opioids for chronic pain that serves as a resource for primary care clinicians.

I also want to make sure my slide is moving. Okay. I guess it is.

What is the analytical file? I need to switch the order of the bullets a little bit. First of all, NDC stands for National Drug Code, which I'm sure most of you are familiar with. MME, as we already heard many times in the morning, stands for morphine milligram equivalent.

The file basically contains all FDA approved opioid medications, both current and those that are

Page 198

already off the market, for instance, for processing. The file is organized and sorted by NDC numbers of the drug. In addition to NDC, it also contains drug names, both brand and generic; strength of the opioid ingredient; DEA schedule; et cetera; and of course the linked oral MME conversion factors.

The file has been available since around 2014 and has been updated annually. The major reason for the update is to add new NDCs of opioids every year.

This is a sample screenshot of the analytical file where all the drugs – or in other words, all the NDCs -- are hydrocodone. Just for illustration purposes, as you can see, the information we have includes the NDC product name or the brand name; generic name; master form of the drug; DEA schedule; strength of the opioid ingredient; and the linked or assigned MME conversion factor.

Next, I want to highlight some features of the file. It is a pretty comprehensive list of

Page 199

opioid NDCs, where we try our best to make it comprehensive. It currently contains over 15,000 NDCs, both active and deactivated. It provides essential information of the drugs; for instance, as you saw in the previous screenshot, product name, generic name, strength, et cetera.

When the opioid is a combination of opioid and other ingredient, we separate out the strength of the opioid to make the use of the file easier. Oral MME conversion factors were assigned to each NDC, and we also provide documentation with detailed information on the purpose of the file, our exclusion criteria, instructions for use, and some important caveats.

So where do we obtain all this information to compile the file? We use RED BOOK from IBM, which is the commercial drug product database that provides a detailed description for over 300,000 prescriptions and over-the-counter pharmaceutical products. Virtually, every drug product approved by FDA for manufacture and distribution appears as a record in the RED BOOK database. The database

Page 200

uses NDC as a unique identifier for each drug record.

The ultimate source of the NDC, of course, is what is being published by FDA in the NDC directory. At CDC, we receive the records annually. In addition to the drug information, we obtain oral MME conversion factors from the literature.

Here are three major ones we have been referencing. In the morning, Dr. McPherson made some great points about the reference. The Von Korff study is the first one we used when the file was first developed or compiled around 2014. Later during the annual updates, we added and consolidated additional references.

I think we all agree this is very complicated, as we heard in the morning many, many times. Probably not a single reference can provide all the conversion factors for all types of opioids, all purposes, and all applications.

This slide is to show you where to request access to the analytical file. The requester has

Page 201

to provide information for what purpose they will use the analytical file, whether it's for research or surveillance, and to what type of data they will link or merge the analytical file. We included a link here.

Moving on to the second item on the agenda, I'm going to focus on the purpose of the analytical file and the process of developing or compiling it. As I mentioned, the file first became available around 2014. About two to three years prior to 2014, when the opioid overdose epidemic started drawing more national attention, there was also a growing amount of surveillance and research on prescribing pharmaceutical opioids; for instance, studying the trends and patterns of prescribing and association between opioid misuse and overdose.

I think in the morning Ms. Corinne Woods' presentation really covered this very well. When the slides become available, I think you can refer to some contents from her slides.

More than [indiscernible], the major data being used for this type of research and

Page 202

surveillance are large outpatient pharmaceutical claims and pharmacy transaction data, including safety DMPs. As a result, there was a need to identify opioid prescriptions from this data. I will explain later why this is needed.

There was also a need to retrospectively calculate dosage of prescribed or dispensed opioids by converting dosage to standard MME for research and surveillance purposes. We developed this file trying to meet these two needs, and from the very beginning, we emphasized that the analytical file is intended as a data resource for research and analytical purposes or surveillance monitoring of population level drug utilization.

The analytical file is not intended for any clinical decision making by clinicians while prescribing opioids. The oral MME conversion factors included in the analytical file do not constitute any clinical guidance for prescribing or recommendations for converting patients from one form or another, which we heard a lot in the morning about the capacity for doing that.

Page 203

I mentioned two needs earlier, so now let me explain what need number one means here; identify opioids from claims or pharmacy transaction data. Here is a screenshot of a typical outpatient prescription claims data set. For reimbursement purposes, dispensed medications and claims or pharmacy transactions used NDC as the identifier. Other information would include dispensed date, dispensed quantity, day supply, treatment, and some information about the patient; for instance, age and sex, et cetera.

Other information of the drug or of that NDC are not always available, so we don't know which are opioids and which are not. Even if we know which are opioids, what is the strength of a dispensed medication, and for that opioid prescription, what is the MME conversion factor? Why do we need this additional information? Because only with that can we retrospectively calculate the prescribed daily dosage, the MME, for research and surveillance purposes. For illustration purposes, in this screenshot for

Page 204

instance, the number one NDC is indeed an opioid prescription.

We know what our needs are; we just need to find this information. More importantly, we need this information at the NDC level. In other words, the NDC has to be the drug identifier so that we'll be able to link this information to the claims data or pharmacy transaction data.

So now we're circling back to the data sources we use, the RED BOOK data. It contains the information we need and uses NDC as a drug identifier. By using the RED BOOK and MME conversion factors obtained from the literature, we are able to compile the analytical file.

But here is the question. As I mentioned earlier, RED BOOK data contains more than 300,000 drug product records. How do we identify opioids from the RED BOOK accurately?

Again, here is a screenshot of the RED BOOK data. This is, again, for illustration purposes, as the RED BOOK data contains much more information for each NDC record, so this is only part of the

Page 205

data.
We identified opioids by using therapeutic class 60, 61, 62, where 60 contains opioid agonist, 61 contains opioid partial agonist, and 62 only contains tramadol. In this screenshot, again, you can see several opioid products here, including oxymorphone, oxycodone, and hydrocodone. There are many therapeutic classes accounting for these over 300,000 NDCs, but opioids are the number one in terms of its number of NDC codes.
Some additional steps we took, based on the purpose of the file, we excluded opioids that are typically used in non-outpatient settings, including injectables. In other words, patients don't normally get this dispensed at retail pharmacies.
We also excluded opioids for cough and cold formulations from the list. More importantly, we separated out the strength of the opioid ingredient when the drug is a combination of opioids and other components, which is very common for opioid medications, as you can see in this screenshot.

Page 206

Based on the opioid ingredient, we assigned the type of opioid -- for instance, hydrocodone, oxycodone, tramadol, fentanyl -- to each individual NDC. Next, we assigned the oral MME conversion factor to each NDC based on what type of opioid it is. Here is an example of the conversion factors we used.
For most opioids, it's relatively straightforward to assign an MME conversion factor. I only say "only" relatively for the purpose here, however, for some it's much more complicated. For instance, fentanyl has different forms of drugs. As a result, different conversion factors need to be applied.
In the screenshot I'm showing here -- this is from RED BOOK data -- you can see fentanyl transdermal patch. There's also fentanyl film, and fentanyl lozenge. They have different conversion factors, and it's even more complicated for the fentanyl transdermal patch, which was covered by Dr. McPherson and I believe Dr. Fudin as well this morning.

Page 207

For methadone, of course -- again, you heard it this morning from previous speakers -- the conversion factors might depend on the dosage of the methadone in milligrams. The more the milligrams of methadone, the higher the conversion factor. We applied the conversion factor of 3 for the purpose of the analytical file, which I will explain later on.
Here is a screenshot of the compiled NDC and MME analytical file. The file basically just looks like this. When users have access to the file, we deliver the file itself in Microsoft Excel, as well as the SAS data file. We also include the SAS program so that the user can use it to link the analytical file to their pharmaceutical claims data or pharmacy transaction data.
In terms of maintaining the file, again the annual update. The major reason is to add new NDCs for opioids every year. It's been decreasing in terms of the number of new NDCs, but it's probably around 115 new NDCs every year.
Now that we have the file, let's talk about

Page 208

how to use it. Going back to the screenshot of typical pharmaceutical claims data or pharmacy transaction data, this is the information that is normally available. The only identifier is this NDC code. When you first receive the data, you don't know which drugs are opioids. When you use the analytical file, to join or merge the analytical file with your own data, either claims or pharmacy transaction data, using the NDC has the key for the merge.
Here is a screenshot of your own data after the join or merge. On the left in the blue box is the information from your own data. On the right in the red box is the information you merged into your own data that is from the analytical file.
First of all, now we can tell which prescription claims are opioids. As you can see, only the records with information of generic drug name, or strength, and conversion factor are opioids. We use all this information, plus the dispensed quantity, and day supply you already have from your own data, and you can calculate

Page 209

retrospectively the prescribed daily dosage of that prescription.

How to calculate the prescribed daily dosage, the goal of the analytical file is that the user can apply one formula to calculate the prescribed daily dosage with both information from the claims data or pharmacy transaction, as well as information being merged into the data, which are, of course, the dispensed quantity day supply and the strength of the opioid ingredient and the MME conversion factor.

Here on the top of the slide I'm showing the formula for calculating data MME. If you compare this screenshot with the last one, the difference is there are additional columns and of the data, showing you the calculated daily dosage for that particular opioid prescription. For instance, the first one, hydrocodone, prescribed quantity of 120 tablets; strength, 10 milligrams per tablet; so the calculated daily dosage is 40 MME per day.

Again, it could be complicated, particularly for the fentanyl transdermal patch and methadone.

Page 210

Let's use the fentanyl transdermal patch as the example. The fentanyl transdermal patch and also the most prescribed fentanyl requires special consideration when calculating daily dosage because the measure of the strength is micrograms per hour.

Here is a screenshot of real claims for the fentanyl transdermal patch. If you recall, when we talk about extending conversion factor to opioids, the fentanyl transdermal patch should be 0.1 multiplied by 24, meaning that 0.1 micrograms of fentanyl is equivalent to 1 milligram of oral morphine. Multiplied by 24 means 24 hours in a day, so it should be 2.4.

Using the 25 microgram per hour of fentanyl as an example, if we want to apply the formula directly, we need to do further adjustment, which is to take into account that one patch will be used for 3 days, which is 72 hours. So the value in the red box is the conversion factor of the fentanyl transdermal patch in this particular context. When you work with the analytical file and work with claims data, you apply the formula directly. We

Page 211

have this documented in detail together with the analytical file. So when we apply this value, then we would calculate the daily dosage of this 25 micrograms of the fentanyl transdermal patch as 60 MME per day.

So again, continuing to show the fentanyl transdermal patch as an example, the screenshot here, the difference is there are two additional columns. One is showing the conversion factors we use for this analytical file, as well as the calculated daily dosage.

I thought it was interesting to point out the 75 microgram per hour because it was also used as an example by Dr. McPherson and Dr. Fudin this morning. The formula here calculates the daily dosage for the 75 microgram per hour as 180, I believe which is in the range that the presentation this morning showed, but probably at the upper end.

For methadone, for the purpose of using the file, we applied a conversion factor of 3 so that the formula can be applied directly. Again, this is for the purpose of research, surveillance, or

Page 212

monitoring population drug utilization of opioids. It's not a sliding conversion factor here, however, we also want to show you some real methadone prescription data we just obtained from IQVIA, the National Level Dispense Data of 2019.

Methadone prescriptions account for about 1 percent of total opioid prescription, excluding buprenorphine for MOUD in 2019. So 1 percent, that's about 1.45 million prescriptions in 2019. Interestingly, when you look at the distribution of strength per unit among all the methadone prescriptions, the 5-milligram tablet accounts for about 24 percent, and the 10-milligram methadone accounts for about 76 percent.

So they basically account for all of the prescribed methadone prescriptions in 2019, which means if you look at the daily dosage and micrograms for methadone among all the prescriptions, the daily dosage would be an incremental of either 5 milligrams or 10 milligrams. We think this is important for calculating the conversion factors for methadone in

Page 213

a clinical setting and also helpful for the discussion, in general, around the conversion factors for methadone.

We are also providing the distribution of daily micrograms of methadone prescriptions in 2019. As you can see, the mean daily and microgram methadone prescription is about 36, and you see all these percentiles. The median is 30 milligram.

Next, I'll just go over the next few slides very quickly. These are some real applications of the file. The first thing is for surveillance purposes, we use the file, then link with pharmacy transaction data to calculate average data MME per prescription, of course, retrospectively, from 2006 to 2015. We calculated county-level prescribed MME per capita for 2015.

Just as an example also, using the analytical file for surveillance purposes, this is another example. This is a web application at CMS. CMS has these tools for users to track state-level prescribing of opioids, as well as the average daily dosage of the MME per prescription amount,

Page 214

either the Medicaid population or the Medicare population.

This is another example of the state PDMP program using the analytical file with their PDMP data to create statistics on their PDMP data dashboard. This particular one is from, I believe, Rhode Island, where they show the number of prescription -- can you still hear me?

DR. CHAI: Yes, I can hear you.

DR. ZHANG: My Adobe is showing connection lost.

DR. CHAI: Gideon, or if --

DR. ZHANG: It's back. Sorry about that.

DR. CHAI: I can see your slide. It's back? Okay. Thank you.

DR. ZHANG: Okay. Great. Thank you for confirming.

This is showing the number of prescriptions over what they found as high-dose opioids. I believe it's over 90 per day. Again, this is retrospectively calculating the prescribed 80 doses for opioid prescriptions in Rhode Island, and it

Page 215

shows the next figure longitudinally from 2017 to 2020.

I believe you can hear me, but I'm still showing that message. I'll just keep moving.

The next slide, I'm trying to show some examples of published studies, mainly research, using the analytical file together with pharmacy claims or pharmacy transaction data for all these research topics.

This is only a very, very small portion of published studies using the analytical file. There are tons of more studies out there looking at prescribing patterns, as well as, most commonly, associations between prescribing or use and overdose, as well as other adverse health outcomes.

Lastly, I want to go over some important distinctions between the analytical file and the table of MME conversion factors we published with the CDC prescribing guideline. Again, the analytical file is not intended for any clinical decision making by clinicians, particularly primary care clinicians, when prescribing opioids.

Page 216

The conversion factors we included in the analytical file should not be used directly by clinicians to calculate daily dosage for patients. I think the methadone is a great example, as well as the fentanyl transdermal patch. The MME conversion factors in this file do not constitute any clinical guidance or recommendations for converting patients from one form of opioid analgesics to another.

For clinical decision making, in March 2016, CDC released the guideline for prescribing opioids for chronic pain. We also developed and published the guideline to provide recommendations for prescribing opioid pain medication for patients 18 and older in primary care settings.

The recommendations focused on the use of opioids in treating chronic pain in all patient settings, so the guideline is not intended for patients who are in active cancer treatment, or palliative care, or end-of-life care, which we covered a lot this morning as well.

The CDC guideline addresses patient-centered

Page 217

clinical practice, including conducting steroid assessments, which speakers this morning also emphasized; considering all possible treatment; closely monitoring risks; and safely discontinuing opioids, which, again, I think the Q&A early afternoon was touching on this topic.

The guideline includes 12 recommendation statements. Particularly, I want to point out that we emphasized in the prescribing guideline, when opioids are started, clinicians should avoid increasing dosage to over 90 MMs [ph], work carefully to justify a decision to titrate dosage to more than 90 MMs per day. However, this recommendation has been misapplied, and this recommendation doesn't suggest discontinuation of opioids already prescribed at higher dosage.

Improving the way opioids are prescribed through clinical practice guidelines can ensure patients have access to safer more effective treatment while reducing the number of people who suffer from opioid-use disorder or overdose from these drugs. At CDC, we aim to save lives and

Page 218

prevent prescription opioid overdose by equipping providers with the knowledge, tools, and guidance they need.

As I mentioned earlier, published together with the guideline, there's a table of commonly prescribed opioids, which you are seeing here on the slide. We also want to point out these opioids represent approximately 99 percent of opioids prescribed in the U.S. or dispensed from retail pharmacists in the U.S., excluding tramadol.

We want to emphasize that a guideline table should not be used to calculate dose and MME to determine dosage for converting one opioid to another, which we included together with this guideline table for a clinician to note or consider. To help support uptake and use of the CDC guideline, we also developed communication and translation materials to help make the guideline more interpretable and accessible.

Another resource we created is the free mobile app for these commonly prescribed opioids you saw in the previous slides. This app includes

Page 219

an MME calculator, a summary of key guideline recommendations, and also a link to the full guideline recommendations. There's also an interactive motivational interviewing feature that can help the provider to practice effective communication skills and prescribe with confidence, which, again, I think during this morning's presentations, speakers emphasized about educating patients about coping with pain, et cetera. At the bottom of the slide, we included a link to the mobile app, if you're interested.

With that, that will conclude my presentation, and thanks for your time. And again, thank you for the opportunity.

DR. CHAI: Thank you, Dr. Zhang. That was very helpful, and thank you for illustrating the great deal of work that you've been doing in this space, and your colleagues. We appreciate continuing to advance the science with you in this space.

DR. ZHANG: Thank you.

DR. CHAI: Yes, thank you.

Page 220

Next, we will be hearing from Dr. Pittaway-Hay, followed by Dr. Molinari, calling in from a very late hour from the United Kingdom. We're very thankful to have you here to provide insight into the medicines and healthcare products' regulatory agencies' perspective on MMEs.

DR. PITTAWAY-HAY: Just checking. You can hear me?

DR. CHAI: Yes, I can hear you. Thank you.

DR. PITTAWAY-HAY: Wonderful. Thank you.

Presentation – Justin Pittaway-Hay

DR. PITTAWAY-HAY: Thank you very much for inviting me to this talk. Thank you. It's a great pleasure to speak to you on the MHRA's perspective on some work that we have been doing in relation to MME tables. Of course, just the customary disclosure slide; these views are of the speaker and are not necessarily of the MHRA.

As a quick overview, I'm just going to give you a quick view of what the MHRA is, an opioid expert group; the problem statement that we had proposed to us; the objectives and approach that we

Page 221

did to look into some of this work; some very high-level results that we did; and also I'm going to touch on some discussion and, of course, limitations, which have been actually discussed in some of the earlier slides. Then my colleague, Dr. Molinari, will discuss some of the clinical implications of this research or what these findings are.

The MHRA, the Medicines and Healthcare Products Regulatory Agency, we regulate medicines, medical devices, and blood components in the UK. We are essentially the UK version of the U.S. FDA. Within the MHRA, we have an independent Commission on Human Medicines, which is I guess roughly equivalent to one of the U.S. FDA committees, and we advise ministers from the government on the safety, efficacy, and quality of medicinal products.

As part of the Commission on Human Medicines, we also have an opioid expert working group which convenes at certain points as a working group as opposed to a standing advisory group.

Page 222

This is a little bit akin to a U.S. panel.

The Opioid Expert Working Group most recently reconvened in early 2019 in light of the growing concerns about opioids, the overuse and misuse of opioids, and particularly in non-cancer indications. This was leading to a growing problem of dependence and addiction which was seen in the UK, which is, of course, seen in other jurisdictions equally.

The remit of the Opioid Expert Working Group was to review the available evidence on opioid dependence and addiction and recommend ways to strengthen risk minimization measures, and to improve communications and education of healthcare professionals and patients.

The members of the expert working group in the UK are made up of various experts in various scientific disciplines across some pain management, nursing; pharmacy; anaesthesia; old-age medicine, as well as medicine in children; and a lay member as well; and also, of course, a pharmacologist.

I would just like to highlight that I am not

Page 223

a member of the expert working group, but I'm within the MHRA, so we work together closely with the expert working group, as they are an independent group from the MHRA.

The problem statement that we had posed for us was the expert working group had to consider what further research was required to investigate the benefits and risks behind the settings of a maximum MED, the evidence supporting the maximum daily dose for which benefit-risk may be favorable, and the calculation of morphine equivalences.

I think this is, of course, seen in some of the other slides as well. It's familiar to everyone, of course, how to calculate the opioid daily dose, but I guess the important thing here -- the RED BOX conversion, that's the crux of the issue here, maybe, of how do we convert those morphine equivalent doses, and of course we come back to the classic aphorism that "all models are wrong, but some are useful." But again, that comes down to what is the purpose.

I guess earlier in the day, it was that

Page 224

clinical practice is a guide for opioid switching potentially, however, this has been, I guess, used as well for other purposes, and that is just to calculate the oral morphine equivalent dose and see whether we can benchmark that and use that for prescribing, as well as looking at total opioid doses. Of course, in other purposes, it may be used for insurance purposes in the U.S.

What we intended to do was identify the opioid conversion tables that were available to us from regulatory institutional guidelines and look at some of the online calculators that were available, and also to review the dose reduction recommendations with formats and the references associated with them.

Secondly -- and this is what Dr. Molinari will go into with more detail -- was to review the recommended maximum MED thresholds from the regulatory agencies and other organizations as well, so I'm going to focus on that first topic there.

We looked at opioid conversion tables of

Page 225

what was available and some of the literature behind them. I say here the literature is based on palliative care, and cancer-related pain is generally not included, although I can say that it probably did slip through a little bit. The sources of data to conversion tables were not critically reviewed, and I think that has been discussed somewhat in some of the earlier talks as well.

Here are the headline results. I will say the table is not intended to be legible per se. There was a lot of data on here. I'll go through the table in the next few slides. Also, I'll say that the explanatory footnotes that were associated with this table and the sources are not included. They would have taken up two to three times as much as the table itself with the explanatory footnote.

But as said, there were a variety of different routes of administration that were identified, so the top perm group is for oral administration. One of course was sublingual, which is of course buprenorphine; rectal

Page 226

administration, again one reference for that; transdermal, skin applications with fentanyl and buprenorphine; as well as parenteral, so injections, whichever method.

At the top, we can see that we have the different sources of information that we found. Of course this wasn't a structured literature review because we did include some online calculations that we did find, and it was also from a couple years ago, so that recent calculator from the CDC is not included. However, we identified 13 different sources in this table. One of them most recently added the Curtis paper there, which wasn't presented to the EWG.

There were 10 different tables identified, one with an associated app. That would be the Australian-New Zealand FPM calculator. There were three calculators identified, and we also included information from SmPC. That is what the UK equivalent is for prescribing information. Some of our opioid prescribing information SmPCs included some conversion factors as well.

Page 227

It is important -- and it was heard in talks as well by Professor McPherson -- the quality of the references. We did a very light-touch look at these of course. We didn't go into detail of the background of them, but we looked at the tables themselves, just the quality of the conversion tables themselves.

Only one of them had individual references, so that H conversion factor. It was linked to a paper. Five of the papers had what we termed "group references" or essentially a multiple-source reference, so there were four or five different references scripted at the end of the table. One referenced a separate source, so one of them actually just referenced another table. I guess somewhat concerningly, six of them -- so nearly a half of them – provided no references as well.

Again, these are some of the headline results that we identified here. The consistency of conversion was also a bit of a mixed bag, you could say, and lacked coding. At the top row there, you can see, and hopefully somewhat a little

Page 228

bit legible, there is some consistency in the conversion rate. However -- and it's been identified in most of the main talks -- the methadone, of course, has variability that is known, and that was highlighted in many of the different footnotes.

Then you can see there's a concern, or a blessing in some way, that some of the tables had ranges. Of course the scientist in me says that a point estimate is sort of worthless without a confidence interval. I guess that may be true here. A range speaks to there might be kinetic differences or differences in what the patient experiences. However, for the purposes of identifying a maximum or a certain point, of course it becomes more difficult. So I guess there are pros and cons to that.

The last bit and what can be seen on the table here is the missing data. Some of these tables, I guess you could say, though incomplete, they didn't refer to -- maybe it was a judgment call by the tables whether they included data or

Page 229

not, but there was a lot of information missing from the tables. Whether that may have been due to non-prescribing in that jurisdiction or in that country, or for other reasons, it wasn't looked into any further.

I'll be very quick on this slide. This is about dose reduction because the purpose of our talk was more to identify a maximum or a total daily dose, and this has also been discussed in earlier talks as well. But most of them included some sort of warning of how to do a dose reduction; that there needed to be a dose reduction in most cases, and especially when giving at high doses.

As I said, most of these tables we identified, they were accompanied with notes for consideration. Some of the examples we've discussed in earlier talks as well that there was caution needed when using it for opioid switching. We needed to consider the variability in pharmacokinetics, so that's how the body handles the medicine, and pharmacodynamics, that's how the medicine affects the body both within and between

Page 230

patients.

Modified-release formulations needed to be accounted for, and data may have been derived from pooled data, and of course residual drug in the patient's systems must be accounted for. So these were some of the examples that were associated with the tables that we identified.

Again, this was highlighted by Professor McPherson's talk as well, this directional inequality. But many of the reviews or tables actually noted that opioid conversion tables may be overly simplified and that clinicians need to be aware that there is that directional difference in opioid equivalents, and that just can't be reversible in any direction.

Many opioid conversion tables included some indication of a limitation to their own table. They said there was failure to standardize to reference opioids. There is also an inclusion of a wide range of doses, and they are sometimes determined by single doses or acute pain, which of course makes them inapplicable for multiple

Page 231

administration settings. It's also been highlighted that sometimes computations have been used instead of clinical trial data.

Published opioid equivalence tables of course provide a clinically useful tool for clinicians, but they have been known to be beset with limitations. We know that there are limitations in them, and they are known, in regard to the underlying data, to have issues of directionality and ease of use. Of course, a patient may be on many different opioids, and adding them all up for a busy clinician may be difficult. This is why we see more and more calculators and online calculators, and now I guess with apps as well.

There is also wide variability in conversion factors between tables and studies that need to be identified. Subsequently, this has therefore an impact on recommending a total maximum and total daily pure dose, which my colleague, Dr. Molinari, will talk in a little bit more detail in the next talk. Thank you very much.

Page 232

DR. CHAI: Thank you, Dr. Pittaway-Hay.

If we can just transition to Dr. Molinari.

Thank you, Dr. Molinari.

DR. MOLINARI: Thank you. I hope you all can hear me clearly. Can you hear me?

DR. CHAI: Yes, I can hear you.

Presentation – Maria Molinari

DR. MOLINARI: Good afternoon, everybody. Thank you to the FDA for inviting us to this workshop and to be able to hear from all the experts in the field of pain. Justin looked at the conversion tables, and my job was to look at the potential maximum daily dose of morphine equivalents and how we can improve the information for prescribers.

The question on the need of a maximum morphine equivalent dose per day was first discussed in an opioid expert working group meeting in June 2019. It was noticed that a number of guidelines on the management of chronic non-cancer pain provided inconsistent information with the maximum morphine equivalent daily dose beyond which

Page 233

the risk of serious adverse reaction, including dependence, exceeded the benefit of pain relief.

The expert working group considered that further research was required to provide evidence in support of a preferred maximum daily dose for which benefit to risk may be favorable and also on the calculation of morphine equivalents.

Justin and I were asked to prepare a paper that could provide an overview of the current situation on opioid equivalent tables and maximum daily dose recommendation for non-cancer pain. The review looked at different guidelines for chronic non-cancer pain in the UK and worldwide. And as I said before, these guidelines provide inconsistent information on the maximum equivalent dose of morphine.

For example, with the first two updates to the guidance, the U.S. Department of Health in 2016 suggested to reconsider the individual benefits and risks when increasing the dosage above 50 milligrams of morphine equivalents a day and avoid increasing dosage more than 90 milligrams per

Page 234

day, or carefully justify the decision to titrate dosage to 90 milligrams a day.

In 2017, the Canadian Practice guideline also restricted the prescribed dose to less than 90 milligrams morphine equivalents a day. The Australian and New Zealand guideline provides 100 milligrams of morphine equivalents a day limit above which specialist advice should be sought.

In the UK, more recently, the Scottish Intercollegiate Guidelines Network was updated in August 2019 and is now recommending a new high limit of 90 milligrams, or even 50 milligrams, which is in line with the CDC.

This is a table, and we put a table together to try to understand what were the differences in guideline. There was obviously not just the lack of unanimity of what is the safest maximum morphine equivalent daily dose, but also there are a number of conversion charts and opioid calculators available that have shown significant difference now to determine opioid conversion to morphine equivalent doses.

Page 235

What was the outcome of the Expert Working Group? The EWG thought that a ready available conversion table was necessary. Ideally, a conversion table for every individual opioid would be helpful and facilitate prescribers. They also recommended it would be useful to establish a maximum range for pediatric dosing, although it was recognized there were currently no guidelines for treating children with opioids, and the posology calculates the milligram per kilogram at the moment.

We sought the CHM opinion on a proposed maximum daily dose on morphine and equivalents, and tried to find what was the best conversion table available and what was the best way to inform prescribers. We presented many of the papers that were used in the different guidelines to discuss our proposal with CHM. Although there were some differences, they all agreed that it is a substantial risk associated with doses above 90 milligrams per day.

Also, our colleagues from the pediatric

Page 236

[indiscernible], they reviewed the pediatric literature on opioids for the treatment of chronic non-cancer pain. They discussed the lack of evidence for treatment in pediatric chronic and non-cancer pain. Literature reports identified inadvertent poisoning, risk of addiction in adolescents, and no really recommendation for maximum equivalent of morphine dose in patients below the age of 18.

Mainly, they used other conversion factors that often are used critically in children, and there is much less evidence for morphine equivalent dose than for adults, and there are very few studies of opioid equivalents and conversion in the pediatric population. Opioid dosing in the pediatric population tends to be weight based, although flatter [indiscernible] dose is based on age [indiscernible], opioid posology in pediatric obesity, for example, is not well understood.

The Pediatric Expert Working Group concluded that it was inappropriate to extrapolate any adult morphine equivalent daily dosing recommendation to

Page 237

any pediatric age cohort. The AG considered the safety of opioids, particularly long-term use, as being different to adults. For example, adolescents will be more at risk of addiction, and younger children under the age of 12, there could be potential differences in safety, efficacy, and pharmacokinetics. In addition, difficulties in recommending levels were identified for children with raised body mass index.

We had to put some information, and we put information in the UK's Summaries of Product Characteristics, which is equivalent to the U.S. prescribing information and is used by healthcare professionals, like doctors, nurses, and pharmacists.

We proposed this text that has been endorsed by CHM and the Pediatric Expert Working Group. This will go in Section 4.2 of the SmPC, which is the section for posology and method of administration. The CHM agreed to prescribe the required practical tool and clean information to administer the safest possible effective dose of

Page 238

morphine or equivalent. We are trying to maintain also consistency with the most updated recommendation, and yet recognize there are limitations of the opioid conversion data available.

This text we are waiting to implement, so it's ready, but of course we need the morphine equivalents table or calculator to be reliable, and consistent, and obviously would make prescribing much easier. After that, we will contact marketing authorization. All are actually already aware that we are proposing some text. They're only waiting for us to tell them when and what to do. So hopefully this workshop will help us to move forward.

Thank you very much for your patience. I hope you managed to hear me clearly. Thank you.

Clarifying Questions to Speakers

DR. CHAI: Thank you, Dr. Molinari and Dr. Pittaway-Hay. Those were very insightful presentations. We appreciate you, especially staying up late to present for us.

Page 239

At this time, we'd like to transition over to clarifying questions, but I'd like to restate how we're going to be moderating this again.

Please note that what we're asking is to use the raised-hand icon to indicate that you have a question, and remember to clear the icon once you've stated your question. Please wait until you are acknowledged to unmute your phone, and remember to state your name before you speak and to direct your question to a specific presenter. We also ask, for respondents, if you could wait to be acknowledged, as we just want to keep some order to how this is run.

We're not going to be able to go back to specific slides because it may kick us out of Adobe, so we don't want to risk that. So we're going to have to keep the questions verbal, and it would be helpful to acknowledge the end of your question with a thank you or end your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

As a gentle reminder, this is the clarifying

Page 240

questions for panelists or presenters session, so please keep all questions and answers to clarifying questions. We do have panel discussions scheduled for tomorrow, so at this time we'll have clarifying questions. And to note the time, we will be ending at 2:50 in order to have a break for 10 minutes before our public comment session to start at 3 p.m. So we can go until 2:50.

So please use the raised-hand icon if you would like to ask a question. And as a gentle reminder, we are unable to take any questions from the audience. All questions and answers are limited to the invited panelists and presenters.

Dr. Fine, please unmute your phone, and if you could state your name?

DR. FINE: Yes. This is Perry Fine again, and I am very much guilty of not being able to distinguish the difference between a clarifying question and discussion. But given the fact that a number of our panelists and speakers will not be available tomorrow, I do want to raise a question. And if it's too broad a question, Grace, just

Page 241

please ignore it, but I would like to raise it.
This whole discussion brings to mind a quote from 1849 -- and I am not that old, but getting close I think -- when Jean-Baptiste Alphonse Karr said, "The more things change, the more they remain the same."
It seems that every advance in at least epidemiology and science that we're trying to take here keeps beating our heads against the same sort of wall. And I'm wondering -- I'm going to call it a clarifying question -- to all of the panelists, or all the members who have spoken so far, to consider whether in fact there's a different direction that is required to really address both the research regulatory policy, but mostly the clinical application of analgesic equivalency, dating back to Ray Hood's original research back in the '50s and '60s, where we don't seem to have advanced much.
That is the use of a whole different science that would apply to this, and that's the science of decision support, where these very complex

Page 242

variables that include drug-drug interactions, drug-disease interactions, pharmacogenetics, social circumstances, and individual psychology, which are perhaps far more powerful influences than any reductionist application on an equivalency table, may be in fact the way of getting at where you all say you want to go. Thank you.
DR. CHAI: Thank you, Dr. Fine. That is a tough question under clarifying questions.
I'm not sure if anyone can address this, but we can definitely incorporate your thoughts into tomorrow's panel discussions.
Would that work for you, Dr. Fine? It's a very big question that you're asking, and I think it will have to --
DR. FINE: Yes. Grace, I know we're up against time here, but since so many of our panelists or discussants won't be here tomorrow, could we maybe give them a chance to think this through? Because if we're going to go forward, I think we really have to break out of this mold or this inadequate model that we've been following for

Page 243

the last 10-15 years, that really has not allowed us to advance the field very much.
DR. CHAI: Yes. And just to clarify, Dr. Parkinson has also joined us for day 1 and day 2, from MHRA, to help with panel discussions tomorrow.
Dr. Pittaway-Hay or Dr. Molinari, would you like to address that quickly? I believe Dr. Fudin has already dropped off due to scheduling conflicts, but Dr. Bettinger is also available tomorrow to help with questions as well for Dr. Fudin.
Dr. Molinari --
DR. PITTAWAY-HAY: It's Dr. Pittaway-Hay here. I guess just to address the question, we did identify, at least from our perspective, this is a multidisciplinary, multimodal approach. I guess as the UK regulator, of course we can do our one small part in addressing the problem that he has identified. I believe Dr. Molinari may have highlighted it a little bit in her slide.
We've tried to identify what we can do, and

Page 244

that is simply to put things into the SmPC, the prescribing information. But before we can do that, there needs to be -- I can see also the point that this is a so-called reductionist view and can we have one table, but that comes with the simplicity that it's better than nothing, I guess. And there are going to be probably many caveats, not just some caveats, associated with a single conversion table if there is one ever developed.
I think also Dr. Molinari might have said -- I speak a little bit -- I think Dr. Molinari might be having some technical issues with her audio.
DR. MOLINARI: Yes. Sorry. I heard also, but from our point of view, we can only try to help prescribers in the safest way to prescribe opioids. Obviously, it's going to be individual variability, and that will be decided by specialists or by doctors themselves what we can do, and decide to give a guide of what we have found. But obviously, that would be up to the doctor who prescribes opioids to decide what is the most suitable dose

Page 245

for their patients.
Bear in mind, above a certain dosage, the benefit has not been demonstrated, but there are increased adverse events. I think that's what we can do from our side as a regulator.
DR. CHAI: Thank you.
Dr. Cunningham --
DR. FINE: Grace, can I do --
DR. CHAI: Oh, sorry. Go ahead.
DR. FINE: -- a quick follow-up or is there something else?
DR. CHAI: Okay. Could you state your name --
DR. FINE: This is Perry Fine. I appreciate how this is creating some discomfort. I appreciate the objectives, they've been clearly stated, and what we're trying to do to create safer, more effective prescribing for practitioners. But I'm really asking the question about does the science that we have adequately -- will it ever really get there?
I'll quit after this with my last attempt,

Page 246

and then we can maybe take this up tomorrow. But the analogy I would draw to is, for instance, in adult respiratory distress syndrome, we really never made progress in reducing morbidity/mortality until we created decision support, where all these different individual variables would enter into decision making that were above and beyond the capability of a clinician to somehow integrate or synthesize, given the time constraints they have, and once that was applied, tremendous breakthroughs were made.
So I guess my question, really -- and I'm sorry I didn't use this earlier -- to the panelists is, do you really believe the science is ample to direct and get the objectives that we're stating, all of us are stating we want to get to? Thank you.
DR. CHAI: I agree. We've carefully thought about the questions that we are posing to the panel discussions tomorrow, and we hope to bring in a lot of what you are highlighting right now. It's a much bigger topic, and what we're hoping is that

Page 247

the panelists that aren't able to join us today will be able to speak with their representatives who will be able to join us tomorrow.
I just want to make sure that we do try to align with the clarifying questions because the questions you're asking are pretty much the meat of what we're trying to discuss tomorrow at the panel discussions, Dr. Fine, which means that they're excellent questions.
Is there another raised hand? I think Dr. Parkinson perhaps.
DR. PARKINSON: Yes. Thank you. I just wanted to emphasize I understand everything that everyone's been saying. It's exactly what we've been discussing in the whole of the Expert Working Group. There are differences between each individual patient, and that is one topic that's been coming up over and over again in our discussions. Every patient is an individual, so therefore to actually state what an MME is or MED is, is really difficult for that particular patient because you do have to take into account their

Page 248

pharmacokinetics, pharmacodynamics, and things.
So unless you can send that patient off to have their liver functions and all their enzymes characterized before you start treating them, I think we are really stuck. And the only way that we can ask as regulators -- we can't say that thing. That's a guidance. That's a clinical guidance.
We at MHRA just talk about the safety and benefit of a particular medicine. So therefore, what do we put down as a maximum dose? Again, it's individualized for that patient, so it's a really, really difficult question to answer at the end of the day. Thank you.
DR. CHAI: Thank you, Dr. Parkinson.
I just wanted to give some time also to Dr. Cunningham and Dr. Emmendorfer, if you would like to comment. I also have a question for Dr. Dasgupta, if you would like to hold your comments.
Dr. Cunningham, do you have anything you want to say before I turn it over to Dr. Dasgupta,

Page 249

or Dr. Emmendorfer?
(No response.)
DR. CHAI: Dr. Dasgupta, why don't you go off mute and state your question? And then if I see a raised hand from Dr. Cunningham, Dr. Emmendorfer, or others, we will try to address it at a later time.
But go ahead, Dr. Dasgupta.
DR. DASGUPTA: Hi. This question is for Dr. Zhang. This is Nabarun Dasgupta, UNC.
Dr. Zhang, does the CDC analytical file have any recommendations on how to calculate MME per day when prescriptions are overlapping and are not exactly the same time periods? The equations and the examples you showed, how to look at it on a per prescription level; I was wondering if you guys had a particular way you'd prefer to calculate per day across overlapping scripts.
DR. CHAI: Dr. Zhang, would you be able to address that question?
DR. ZHANG: Hi. Kun Zhang from CDC. Thank you for that question.

Page 250

Can you hear me, Grace?
DR. CHAI: Yes, I can hear you.
DR. ZHANG: I want to make sure, yes.
Well, the easy answer to your question is, no, we don't have the guidance or recommendation along with that analytical file for calculating overlapping prescriptions at the patient level. It's up to the researchers normally. I believe you can find a lot of examples from the literature.
Also, as I recall this morning, Dr. McPherson showed a very good example about extended release and IR morphine prescriptions for the same patient. But overlapping from a data perspective, or from a claims or pharmacy transaction perspective, being prescribed by the doctor, probably not for the purpose of concurrent use.
I think that's a great example, but unfortunately, with the data we work with everyday, we don't have that information in terms of the purpose, the justification for overlapping prescriptions or concurrent prescriptions, not to

Page 251

mention what is the circumstances for that particular patient in the data we work with every day. So that's definitely a gap.
But again, to your question, that's a good question, and we don't have that guidance in the analytical file. Thank you.
DR. DASGUPTA: Thanks.
DR. CHAI: Thank you, Dr. Zhang.
I'm getting a prompt from Chidi. I don't see any more raised hands, so at this time we will conclude this session of clarifying questions for the speakers today, and a really, really huge thank you to all the presenters, and the panelists, and the audience for sticking it out with us.
Thank you for your time, thank you for your patience and your flexibility, and thank you so much for just a very vast amount of information that has been deposited for us to digest and to think about as we prepare for the next session, which is the public comment session.
We will take a break for 10 minutes and return at 3 p.m. At this time, I'd like to ask

Page 252

those public comment session speakers if they can stay on to work with the AV team to be able to make sure that your audio is connected.
For all others, we thank you for your time. For presenters, please don't be alarmed. We're going to have to clear the room, the presenter room a bit, in order to allow for the public comment session speakers to be brought into the presenter room. I'm talking virtual rooms obviously; but if you could continue to stay on the meeting to hear the very important public comment session speakers' comments, but you will be moved down to the participant room.
So thank you for your time, and we'll see you in 10 minutes at 3 o'clock; or more than 10 minutes, but 3 o'clock.
(Whereupon, at 2:48 p.m., a recess was taken.)
DR. CHAI: Hello, everyone. Welcome back from the break, and thank you for your patience as we work to ensure that all the connections are running smoothly.

Page 253

At this time, I'll now turn over moderation to Dr. Tamra Meyer, who will be walking us through the public comment session.

Thank you, Dr. Meyer.

Public Comment Session – Tamra Meyer

DR. MEYER: Thank you, Dr. Chai.

Welcome back again, everyone. We're ready to get started. We're about to begin the public comment session. As Dr. Chai mentioned, my name is Tamra Meyer. I'm an epidemiologist and a team lead in the Office of Surveillance and Epidemiology in CDER, and I'll be moderating this session.

There were more initial requests to speak during this session than we could accommodate, so FDA lengthened the public comment session to allow as many people as possible to speak, and we conducted a lottery, a lottery to randomly select 35 speakers to present today.

Since this is a virtual meeting, confirmation to speak and prior audio testing was necessary to ensure that the speakers could be heard during the live virtual meeting, and you

Page 254

heard today that that can sometimes go awry as well. Unfortunately, we did not receive confirmation from all the selected speakers, and some of the confirmed speakers let us know today that they weren't able to join.

So you will hear me note this as I moderate the session. We encourage those who were selected and unable to confirm their participation, those who were not selected to present today, and anyone with comments or materials to share with us to submit them to the docket, so that they can be part of the public record for this meeting.

Both the FDA and the public believe in a transparent process for information gathering, and to ensure the transparency at this public comment session, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the public comment session speaker, at the beginning of your oral statement to state any financial or other relationships that you may have related to this meeting topic or to your presentation. If you

Page 255

choose not to provide this context at the beginning of your statement, it will not preclude you from speaking today.

The FDA and this panel place great importance on the public comment session process, and the insights and the comments that you provide can help the agency and this panel in their consideration of the issues before them today.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this public comment session to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by me, the moderator. Thanks for your cooperation.

Since this is a virtual meeting, I want to review the process for this session. I will call your speaker number when it is time for your presentation. If you provided slides, one of our staff will open the slides for you. You may advance your own slides, but you can also ask for

Page 256

us to advance them for you.

You will see the countdown timer on the screen, and we will start this timer once you start your presentation. When your time is up, I will break in to ask you to wrap up your comments promptly. If you have additional comments that you are unable to provide, you can submit them to the docket so that they become part of the public record, and FDA can consider them with the rest of the meeting materials and discussion that we hear today.

Okay. I think we're ready to move to speaker number 1.

Speaker number 1, your audio should be connected now. Will you please begin and introduce yourself?

DR. SAN BARTOLOME: Thank you.

Good afternoon. My name is Mario San Bartolome. I am the vice chair of the American Society of Addiction Medicine, Practice Management, and Regulatory Affairs Committee. I'm an addiction medicine specialist and a board-certified physician

Page 257

in both addiction medicine and family medicine. I have no conflicts to disclose.

Thank you for the opportunity to offer comment on behalf of the American Society of Addiction Medicine. The use of morphine milligram equivalents, or MME, as a metric to gauge overdose risk can be problematic in the field of addiction medicine because the MME thresholds that indicate higher risk for opioid analgesic used to treat pain do not translate well to opioids used to treat opioid-use disorder, or OUD, and in particular, methadone and buprenorphine.

The CDC guideline for prescribing opioids for chronic pain note that most experts generally agreed that increasing doses 50 or more MME per day increase overdose risk without necessarily adding benefit for pain control or function. Key to this recommendation is the underlying premise that opioids are being used to treat chronic pain, and accordingly, benefits were assessed in terms of pain control and function, and harms were evaluated in terms of overdose risk.

Page 258

Importantly, the benefits and risks of using opioids to treat OUD, either methadone or buprenorphine, should be evaluated differently. Both medications have been demonstrated to decrease overdose risk when used to treat OUD, and both have been demonstrated to improve health and social outcomes.

Equally as important, recommended dosages of methadone and buprenorphine, when used to treat OUD, differ from recommended doses for pain treatment. A usual daily dose of methadone ranges from 60 to 120 milligrams, and evidence suggests that 16 milligrams per day or more of buprenorphine may be more effective than lower doses.

Converting these recommended dosages to MME reveal that they exceed the CDC recommendations regarding MME for chronic pain. The thresholds conflict with methadone and buprenorphine clinically recommended and FDA-approved dosages. Applying MME thresholds designed to minimize overdose-related harm caused by opioids prescribed for chronic pain to opioids used for addiction

Page 259

treatment would have a perverse effect on limiting addiction treatment effectiveness, and potentially increasing opioid overdose deaths.

This nuance may be confusing among policymakers and payers attempting to set policies to prevent opioid overdose by limiting MME, as well as among state medical board officials attempting to enforce clinical guidelines and encourage use of opioid analgesics.

As such, ASAM strongly urges FDA and other authorities to exclude methadone and buprenorphine used to treat OUD from any policies intended to reduce opioid overdose-related mortality by limiting MME. Higher MME of these medications are necessary and clinically indicated for the effective treatment of OUD. Thank you very much for your time.

DR. MEYER: Thank you very much, speaker number 1.

Speaker number 2 did not confirm their participation for today, so we will now move to speaker number 3.

Page 260

Speaker number 3, your audio should be connected. Please begin and introduce yourself. Please state your name and any organization you are representing for the record.

MR. AUBRY: Could they put up my slides also?

Good afternoon. My name is Larry Aubry. I would like to thank the FDA for this opportunity. I have no conflicts to disclose.

Opioid doses above 90 MME per day are labeled as high risk due to the disproportion and association -- in other words, direct correlation -- with addiction abuse and overdose deaths. We have cut prescriptions above 90 MME by over 70 percent over the last decade.

As you see the linear regression model for treatment admissions as a function of prescriptions above 90 MME, you would expect a positive direct correlation if we're basing policy on reducing prescription opioids as a means to cut treatment admissions and overdose deaths. Instead, we have a correlation in excess of negative 90 and understand

Page 261

that a value of negative 1 is a perfect inverse correlation.

Next, we do a model of comparing a prescription opioid death as a function of prescriptions above 90 MME, and though the model is not as, let's say, clean as the other models, the key is that, again, it's not a positive direct correlation; it's negative. It's inverse.

The next slide is any opioid overdose death, meaning illegal drugs, too, because many people will say, hey, taking prescription opioids leads right to overdose deaths from heroin and other illegal drugs; again, negative correlation. The next one is total overdose deaths, and again, significantly negative correlation, and in fact our overdose deaths are now above 90,000 for this year.

In conclusion, I'd like to say that, basically, even when you look at simple linear regression, it illustrates the fact that the patterns are inverse and, basically, it's not just science; it's common sense. There's no direct positive correlation. We need to stop measuring

Page 262

success in tapering and discontinuation and stop the subordination of patients rights.

Basically, 18 million Americans are being subjected to this force and coerced tapering without consent. Patients need this medication for functionality, and their families also need it so that we can function as a group. There's no logic. The data shows an inverse correlation. It's not a positive direct correlation. Thank you.

DR. MEYER: Thank you very much, speaker number 3.

Our next speaker is speaker number 4

Speaker number 4, your audio should be connected now. Will you begin and introduce yourself? And please state your name and any organization you are representing for the record.

MS. OGDEN: Please put my slides up. Thank you.

Good afternoon. My name is Kristen Ogden, and I am co-founder of Families for Intractable Pain Relief. I have no financial issues to disclose. I speak today on behalf of a very small

Page 263

subset of chronic pain patients who suffer from severe constant, incurable pain with cardiovascular and endocrine complications. When undertreated, such pain has devastating effects on cardiovascular and endocrine systems, and can lead to premature death.

From the perspective of these patients and their families, MME-based policies have not worked. There are many variables, and patient response varies widely. MME thresholds established in policies have most often been used to set dose ceilings and reduction targets. The result has been an increase in patient harm, not improvement in patient care.

MME policies have caused incalculable harm to patients, families, physicians, and pharmacists. They have harmed our country, our citizens who suffer from the constant reinforcement of the opioids are a bad stigma that fosters loss of empathy for fellow human beings and irrational fear of opioid drugs and the people who use them.

High doses are indeed needed by some

Page 264

intractable pain patients as a last-resort treatment when all else has failed. These patients often suffer from extremely painful, incurable diseases that involve neuroinflammation, such as arachnoiditis and connective tissue disorders, such as Ehlers-Danlos syndrome.

Efficacious doses for some of these patients are in the 2000 to 3000 MME range. If success is achieved with a high-dose opioid treatment regimen, if goals are met for pain control, functional capability, and quality of life, patients should not be tapered off medications that work for them.

The bottom line here, MME should not be used as a threshold for prescribing or dispensing medications or for targeting and disciplining doctors. We need to restore physician discretion to diagnose and prescribe. Failure to do so will allow the continuation of preventable harm. In effect, this amounts to torture of intractable pain patients.

This man is my husband, Louis Ogden, who has suffered pain since the age of 6. After decades of

Page 265

attempting treatment with many modalities, many medications, and many therapies, he started high-dose opioid therapy in 2010 at the age of 60. From 2010 to 2018, he had excellent pain relief with no dose escalations and his best quality of life as an adult.

Then his pain medication dose was reduced because 2900 MME was too high. He no longer has excellent pain relief, improved function, and good quality of life. He should not have to suffer because of an arbitrary number, the MME, is too high. Freedom from pain to the extent achievable is the most fundamental of all human rights. Thank you for the opportunity to comment.

DR. MEYER: Thank you very much, speaker number 4.

Is speaker number 5 still connected? Can you hear us?

(No response.)

DR. MEYER: Okay. I think we're having some technical difficulties with speaker number 5. We'll come back to them at the end.

Page 266

Speakers number 6 through 8 unfortunately could not confirm their participation for today, so our next speaker is speaker number 9.

Speaker number 9, your audio should be connected now. Will you begin and introduce yourself? And please remember to state your name and any organization you are representing for the record.

MS. BUCK: Hi. My name is Shirley Buck. I'm representing American Pain and Disability Foundation. I have no financial associations to disclose. I'd like to say thank you very much for the opportunity to speak with everyone at the FDA.

I'd like to let you know that the 90 morphine milligram equivalency was created out of the blue. There is no scientific proof about it; none. There is no testing, no nothing, it's just out of the wind created.

This is not fair to chronic pain patients. Many, as the last speaker said, are on much, much higher doses. They've lost their entire lives, their homes, their jobs, their families, and

Page 267

everything. That is not how you treat a human being, especially when they're ill or have been injured permanently.

Here's a good example. Imagine if everyone was directed -- and this includes everyone at the FDA and all chronic pain patients -- to only be allowed to wear a size 4 pants. Even if it didn't fit, you still had to wear them. It doesn't work. Do you understand what I'm saying? I hope you do. Hopefully, I'll leave that with you to think about.

The cost effectiveness with pushing everyone on to buprenorphine and Suboxone, even for chronic pain patients, they're putting chronic pain patients on Suboxone. The drugs are astronomically high when you compare it to the usual opioid medication.

I lost my place; I'm sorry.

Illicit drug overdoses are up 1400 percent, not prescription opiates. That is about as low as you can get, besides zero. The chronic pain patients haven't done anything wrong, but yet their lives have been completely put in turmoil. Many

Page 268

have committed suicide just like our veterans. They're going through the same thing. Most of them have been completely cut off. These are our veterans. What is wrong with America? Geez! Some of them are quadruple amputees. They can't get pain medicine. It's inexcusable; it's inhumane torture.

I would seriously like to ask for everyone at the FDA to highly consider getting rid of the 90 MME limit. It's just not feasible for most patients in chronic pain, and it isn't a way to treat pain for anyone. I wouldn't wish this on anyone. Thank you for the opportunity to speak.

DR. MEYER: Thank you very much, speaker number 9.

I believe we have speaker number 5 connected. Can you confirm that you can hear us and we can hear you?

(No response.)

DR. MEYER: Speaker number 5, can you say something?

(No response.)

Page 269

DR. MEYER: Okay. I think we're still having some technical difficulties with speaker 5 --

MS. DIFILIPPANTONIO: I'm here.

DR. MEYER: Oh. Can you say that again?

MS. DIFILIPPANTONIO: I'm here.

DR. MEYER: Okay. Hi. Your audio is connected. We can hear you. Will you go ahead and begin and introduce yourself? Please remember to state your name and any organization you are representing for the record.

MS. DIFILIPPANTONIO: Speaker number 5 is here.

(Pause.)

AV TECH: Carrie, you can go ahead.

MS. DIFILIPPANTONIO: Can anyone hear me?

AV TECH: Yes, ma'am. We can hear you. Can you hear us?

(No response.)

DR. MEYER: Okay. This is Tamra Meyer. Let's go ahead and move on to the next speaker, and see if we can get Speaker 5's audio fixed, and

Page 270

we'll come back to them

Alright. That makes our next speaker, speaker number 10.

Speaker number 10, your audio should be connected. Please introduce yourself. State your name and any organization you're representing for the record.

DR. DeGEORGE: Sure. Thank you. Can I have my slides, please?

My name is Mike DeGeorge, and I'm the vice president of medical affairs of Collegium Pharmaceuticals, a company committed to being the leader in responsible pain management. We felt compelled to comment because we believe the misapplication of MMEs is negatively impacting both patient care and public health, particularly when it comes to atypical opioids, and among those tapentadol, which is a product in Collegium's portfolio.

As we heard from this morning's speakers, the benefits and risks of atypical opioids are not solely dependent on activity at the mu receptor,

Page 271

and as such, MMEs may not provide an adequate measure of dose equivalency.

In addition, atypical opioids have FDA-approved dose limits in their label specific to active ingredients and informed by safety findings. This difference is only partially reflected in the published CDC guideline, as they do not include conversion factors for tramadol or buprenorphine. However, this is not the case with tapentadol.

Taking the CDC conversion factor of 0.4 for tapentadol, as well as the 90 MME recommended dosage limit, the maximum daily dose of tapentadol would be 225 milligrams per day. This is significantly less than the average therapeutic dose of approximately 3[00]-400 milligrams per day identified by phase 3 studies and less than half of the FDA-approved maximum daily dose.

This impacts patient care, as clinicians report a reluctance to prescribe tapentadol based on fear of the optics of having their doses exceed MME limits and concern that they won't be able to prescribe an efficacious dose for their patients.

Page 272

This is problematic beyond the impact of patients, as it also has the potential to negatively impact public health.

Four recent real-world evidence studies have shown that tapentadol has the lowest rate of serious adverse events and no reported deaths in one study. The extended-release version of tapentadol had lower rates of abuse than ADFs and non-ADF ER comparators.

Abuse of tapentadol was infrequent relative to other opioids among individuals entering treatment for opioid-use disorder, and even when comparing to other atypical opioids, tapentadol, a Schedule II product, had lower rates of abuse than buprenorphine, a Schedule III product, on a population basis, and similar abuse when adjusted for utilization. Any artificial barrier to tapentadol prescribing may lead clinicians to drugs that have not performed as well with regard to misuse, abuse, diversion, or overdose over the past decade.

In conclusion, we applaud FDA efforts to

Page 273

examine the science behind MME and their application. We've seen the problems with MME are amplified when applied to atypical opioids, and particularly tapentadol. Real-world evidence related to tapentadol has demonstrated relatively lower rates of abuse, misuse, diversion, and death, and its utilization may be, in part, reduced by an artificially low MME limit, which has the potential to negatively impact public health.

Because of this, we believe tapentadol should be treated like other atypical opioids and should not have a specific MME conversion, and instead prescribers should be allowed to dose the medication as per the FDA approved label. Thank you for your time.

DR. MEYER: Thanks very much, speaker number 10.

Okay. Let's try speaker number 5 again.

Carrie, can you hear us; and say something?

(No response.)

DR. MEYER: It looks like we might have lost her again, so we will try speaker number 14.

Page 274

MS. DIFILIPPANTONIO: I'm --

DR. MEYER: I'm sorry.

Carrie, are you there?

MS. DIFILIPPANTONIO: I am here.

DR. MEYER: Perfect, and we can hear you well.

Okay. Go ahead and introduce yourself. State your name and any organization you are representing for the record.

MS. DIFILIPPANTONIO: My name is Carrie Difilippantonio. I'm a mom, a daughter, and a granddaughter of rare diseases; seem to collect them.

My first encounter with regulating opioids was after a Ganz procedure, which is where they break your pelvis in three places and put screws and cadaver parts in. I was sent home with a script for pain medication, and insurance said, "No. Prescribe this instead." Then after mailing the script, I turned it in, and they rejected that again. For 32 days, I was passive suicide or making plans, and I would just ask for help, can

Page 275

you take me off that. My son has three of my rare diseases, and I advocate for him so that he doesn't have to.

Patients living in the agony hear the words, "opioid epidemic" or "opioid crisis." We get triggered. We have medical PTSD due to medical abandonment, harassment, profiling by pharmacies, laws, doctors, and we are extremely questioned about why we need meds. This means we have to prove to the doctor that we are sick or have this condition, and that's not what it's supposed to do.

I recommend that everybody look at United States House of Representatives number 747, released in December of 2019. It talks about the War on Drugs and how we've gotten nowhere, and that it's just hurting people that are dependent. I'm bed-bound because I don't get pain meds at work.

I just wanted to point out that resolution. And it's 25 things, I think, it says about what government has done and how it hurt us; for example, like Nixon's War on Drugs because him and his sidekick didn't like blacks or any other

Page 276

ethnicities.

At the end of their resolution, they say, "Whereas after almost 50 years, the War on Drugs has yet to achieve its goals, and whereas there has been no formal action by the United States government, abuse and to treat the war on drugs is a health issue. Now, therefore it be resolved in the sense of the House of Representatives." They're not going to pass any more law around opioids.

Another thing that is a big problem is pharmacies. Some of them, I don't know, they just have a God sense. They hold meds ransom. I am a stage 4 breast cancer survivor -- or not survivor but sponsor. Her pharmacist would not hand over the drugs.

Chronic pain is an exemption, and it's been overlooked. We are dependent on it, and one of the [indiscernible] did not want to make statistics, but only six, and this was a peer-reviewed scientific journal that says only 6 percent of patients become addicted. That's very, very

Page 277

important to understand.
Forced tapering and patient abandonment, I was cut off cold turkey from my pain doctor. Then about a week later, my son called 911, and he saved my life because I had 3 to 5 minutes left of life. And while I was waiting for my COVID test to be admitted, I had a series of mini heart attacks, and then a couple weeks after that, a series of strokes. I have lost memory for at least 9 months.
I really hope that the pendulum swings back to the middle because you're really hurting moms, dads, grandpas. My grandma died last fall, and they took away her pain medication and kicked everybody out of the room.
I do have an advocacy group, Pain Awareness Warriors, and we call each other's hospitals to make sure that we're getting the medication that we need. And if they're not --
DR. MEYER: Speaker number 5, I'm so sorry. Your time is up. Can you just please wrap up your comments? Thanks so much. We'll give you another 30 seconds.

Page 278

MS. DIFILIPPANTONIO: Sure.
So patients are calling into other doctors' offices and calling into hospitals to make sure that that patient is cared for, and feels like a human being, and not just thrown away in the trash, which is how most of us feel. So I leave you all with that.
DR. MEYER: Thank you so much for your comments. We really appreciate them and the time coming here today to talk to us.
Our next speaker is going to be speaker 14 because speakers 11 through 13 were unable to confirm their participation for today.
Speaker number 14, your audio should be connected now. Will you begin and introduce yourself? And please remember to state your name and any organization you are representing for the record.
MS. NICHOLSON: Yes. Thank you. Hello. My name is Kate Nicholson. I am speaking on behalf of the National Council on Independent Living, the nation's largest cross-disability organization with

Page 279

centers in every state and territory, and the National Pain Advocacy Center, a new nonprofit that receives no industry funding and advocates for people in pain. I have no conflicts to disclose.
Thank you for the opportunity to speak. Morphine milligram equivalents have become an increasingly important metric. For many pain patients, MMEs now determine what level of medication will be offered or covered, or even whether a patient will receive health care at all. For clinicians, MMEs can be a basis for oversight and a proxy for prescribing that falls outside standard practice or accepted norms. MMEs have become, in effect, a standard of care.
Notably, there has been an uptick in tapering in patients whose MME falls outside dosage guidance in the 2016 CDC guideline for prescribing opioids for chronic pain. Ten to 12 recent observational studies paint a bleak picture of how opioid tapering is happening in practice, including that it often occurs abruptly with negative health consequences and that it may actually increase

Page 280

patient risk of overdose or suicide, in addition to destabilizing their lives.
I hear from patients whose care has been limited, denied, or terminated due to MMEs almost daily. One woman with advanced MS wrote to me to say that she had led a full life on a steady dose of opioids for over ten years, but that her dosage was slightly above the MME recommended in the guideline. Since her doctor has terminated her medication, she has spent the last year entirely in bed.
Another wrote, "My situation has become desperate, as my condition worsened. Sunday, I called a suicide hotline for the first time. My ability to work is drawing to a close. My marriage is in serious trouble. I'm sorry to be so dismal, but I am at the end of my rope."
Forced and abrupt tapering continues despite warnings from the CDC, the FDA, and HHS. Given how consequential MMEs have thus become, we thank the FDA for hosting this session. Specifically, we underscore the concern that variations in drug

Page 281

metabolization, both among medications and from genetic variabilities, are insufficiently accounted for. Also, as one presenter will show, there are flaws in how MMEs are calculated in practice. The same medication given at the same interval could be calculated to have an MME that falls below and above the 50 to 90 threshold.

In closing, we ask that the FDA look closely at the scientific integrity, viability, and continued use of this concept because over-reliance on the MME metric, which is supposed to be used to ensure patient safety, has also proven detrimental to many patients and to patient-centered care. Thank you.

DR. MEYER: Thank you very much, speaker number 14.

Speakers number 15 and 16 did not confirm their participation for today, so we will move on to speaker number 17.

Speaker number 17, your audio should be connected now. Please begin and introduce yourself. Please remember to state your name and

Page 282

any organization you are representing for the record.

MS. BROOKS: My name is Kelly Brooks, and I don't have any financial or conflicts to disclose. Again, my name is Kelly Brooks, and I'm a patient with reflex sympathetic dystrophy, rheumatoid arthritis, and stiff-person syndrome. I have been in pain management for 12 years. I have always struggled with getting the right amount of pain relief from my medication.

For a while, I can manage at my baseline level, at a 6, with my RSD. Unfortunately, I was diagnosed with RA a couple months ago, and now my baseline is an 8. My prescribed dosage does not help me if my pain increases due to activity, flares, or being diagnosed with another disease. I need more medication for those intolerable pain levels, not less. I shouldn't have to cry in bed because I went to watch my son participate in a single sports event. I deserve to participate in life, and I didn't ask for any of these diseases.

For many years, my doctor and I have faced

Page 283

increased pressure to reduce my medication, and MME limits have kept my doctor from being allowed to increase my medication to an effective range. I have led a support group for ten years online for thousands of women with RSD. I hear my story repeated all over the country daily. I watched my own mother with MS struggle with not getting the right amount of medication she needed.

Recently, our support group lost 5 patients in 7 days to suicide, all of them directly related to not being able to get medication or being forced-tapered off their current prescriptions. I knew all of them, and the hardest suicide for me was my friend's young son, Danny Lucas, who was never even given pain meds due to MME and CDC guideline, and he still committed suicide because he couldn't handle the pain.

I truly don't believe there is a future direction for MME. MME is a crazy thought, just a thought. It's fundamentally broken and you can't fix it. It can't be refined or improved by tinkering. MME limits need to be fully repealed,

Page 284

both federally and at state level. It needs to start over from the ground up with reasonable pain management and reasonable guidelines. I believe pain management doctors actively practicing medicine should be making the decisions, not doctors behind a desk at the FDA or CDC.

Pain management is not a one-plan-fits-all treatment. Patients are people. People are different. I will provide a quick example with aspirin. If a 7-foot-4 basketball player takes 2 aspirin and a 4-foot-5 little person takes 2 aspirin, the little person has 4 times the amount of aspirin in their system.

Did the little person take too much aspirin or did the basketball player take too little? Our bodies respond, metabolize, and ingest medication differently. Basing our treatment on MME is disgusting, it's barbaric, and it's quite obviously causing a problem with pain patients and pain management.

In closing, I just would like to say that pain management that is done by actual pain

Page 285

management doctors and not primary care physicians is extremely scrutinized. We are randomly drug tested. I can be called at any point and be asked to bring in my medication and have my pills counted. All my medication is sent electronically to the pharmacist, so I don't know how true pain management patients are even part of or being considered as a loophole to the opioid crisis.

Thank you very much for your time. I appreciate the FDA allowing me the moments to speak, and I hope, for our sakes, you can hear our plea. We are in desperate need of help. Thank you.

DR. MEYER: Thank you for your comments, speaker 17.

Speaker number 18 did not confirm their participation for today, so we will move on to speaker number 19.

Speaker number 19, your audio should be connected now. Please begin and introduce yourself, and remember to state your name and any organization you're representing for the record.

Page 286

DR. ARORA: Hi. Am I audible? Hello? Hello?

DR. MEYER: Hi. We can hear you.

AV TECH: Yes, we can hear you.

MR. ARORA: Hi. My name is Rahul Arora, and I'm a postgraduate in palliative medicine from India. These are my credentials. I think the discussion that we're having is important to discuss this right now. I have no conflicts of interest.

I think we already know about the existing guidelines and what they say. What I am concerned -- and I'm going to take a very different route from what others have said, and this might disturb all these champions who continue to fight against pain. But the fact is that I am deeply concerned by the use of opioids that I see around myself and the exclusion of opioids, which is not proceeding according to plan.

I just saw a patient being escalated from 5 mg q4 hourly to 20 mg q4 hourly in one instance, and I am concerned that guidelines are not being

Page 287

followed. I am not saying that we do not need to use opioids. I know that there are no options, especially in pain conditions like cancer pain, chronic degenerative neurological illnesses, but we also need to be very forthright about discussing their drawbacks. We need to be in a position where we can talk to the patients directly about the impact of opioids on survival and the impact of opioids on, say, the addiction potential of opioids. We need to investigate that, too.

The broad elements of my presentation include whether we need to be including any NSAIDs. There was a talk about atypical opioids, so talking about NSAIDs, when I prescribe opioids and patients are getting NSAIDs, I need a conversion.

Whether opioids have an adverse effect on survival, we do not usually account for incomplete cross-tolerance, which is very disturbing, and there is a lack of options for treatment of acute neuropathic pain, and this could be a reason why opioids are being used indiscriminately.

There is oral morphine sulfate that we use,

Page 288

then inclusion of NSAIDs, spoken about this earlier. There is increasing evidence which talks about the adverse effects of opioids on survival, and these are studies by Boland, et al. and Hasegawa, et al., which say directly that opioids have an adverse impact on survival.

Can we ignore that impact? These are the difficulties with using available options for neuropathic pain, like lack of cardiac monitors in my ward, like the use of midazolam with ketamine for emergence delirium, or the indiscriminate used increments in morphine.

One of the practical issues is inability to account for incomplete cross-tolerance and conversion between various routes of administration. We talk about MED. We usually talk about the oral MED and not the IV or the subcutaneous routes.

Evaluation of complexity of pain control in association with descriptors of difficult-to-control pain on scales such as CHMP that fails to reveal a linear correlation, and there is limited

Page 289

availability of options for breakthrough pain management when transdermal fentanyl is being used for background baseline pain. So number of doses before dose escalation is to be achieved needs to be considered more thoroughly.

We know that when we use rapidly acting oral fentanyl preparations or rapid onset opioids, they might not be oral always, but intranasal formulations, let's say buccal formulations, and when we're using morphine for breakthrough pain -- so when we use IROs versus morphine for breakthrough pain, can we actually equate the concept of morphine equivalent daily dosage?

What are the future directions? We should study opioid dependence in advanced cancer. We should study the role of interventional pain procedures, which then leads to a decrease in opioid doses in the long term; what is the impact on opioids on survival; and we should investigate this as a primary outcome. We should also be studying, in turn, variation pharmacokinetics, which has been demonstrated very clearly in this

Page 290

particular seminar.

I would like to thank you for your time, and I would like to thank the FDA for this opportunity to present.

DR. MEYER: Thank you very much, speaker number 19.

Speaker number 20 did not confirm their participation for today, so we will move on to speaker 21.

Speaker 21, your audio should be connected now. Please begin and introduce yourself, and please remember to state your name and any organization you are representing for the record.

(No response.)

DR. MEYER: Speaker number 21, can you hear us?

MS. WEISMAN: Yes. Can you hear me?

DR. MEYER: We can. Please go ahead. Remember to state your name and organization you are representing for the record.

MS. WEISMAN: Okay. Great. My name is Wendy Weisman, and I'm not representing and don't

Page 291

have any conflicts. I just want to say thank you for giving me this opportunity. I'm grateful our voices will finally be heard and attention is being brought to this crucial topic.

The MME number I feel was originally assigned with a patient in mind that has never been on narcotics, has no health conditions that affect metabolizing medications or tolerance, and for patients who will only be on narcotics short term for an acute injury. This unreasonable expectation has destroyed many chronic pain patients' treatment plans. Here's just some of my stories summarized.

I'm a 34-year-old RN. I've worked hands on with patients since I was 18. As my body broke down and pain progressed, I took a desk job as an RN with an orphan drug program until I collapsed in the middle of the office. I've been officially deemed permanently disabled, and I'm now fighting for quality of life while dealing with crippling pain. I have CRPS or RSD, also known as the suicide disease, and Ehlers-Danlos syndrome. These are labeled as two of the most painful conditions.

Page 292

I was a compliant patient only seeing one physician until my MME score was flagged too high. The 7-plus years of monthly clean drug screens, being on one medication with no increase or change in dose; nothing mattered. I was told on a routine appointment that I had failed my drug screen and was being released. The doctor eventually retracted and said it was a false positive, but it was too late.

Not only did I lose continuity of care with my physicians, but this flagged me as a high-risk patient. Physicians didn't care that it was false; I was a risk, especially with my MME score. Many, including doctors and staff, unfairly labeled and judged me as a drug seeker because of the score. One physician actually said she would like to help me, but she couldn't because of my score. She added that if she were me in that level of pain she knows that I'm in, she would want to die.

This is what pain patients go through. We are judged unfairly and end up with greatly reduced quality of life. This is why many choose suicide.

Page 293

As you're hearing over and over again, we lose people every day.
My pain is still not managed. My quality of life is poor. Please consider making changes. Please hear our voices. Please consider the actual patients and life that we could have. Quality of life can't be quantified in a number. Thank you.
DR. MEYER: Thanks very much, speaker 21.
Speaker 22 did not confirm their participation for today, so we will move on to speaker number 23.
Speaker 23, your audio should be connected now. Please begin and introduce yourself, and remember to state your name and any organization you're representing for the record.
(No response.)
DR. MEYER: Hi. Speaker 23, can you hear us?
(No response.)
DR. MEYER: Speaker number 23, we're having trouble hearing you, so we're going to move on to the next speaker for now and will return to you

Page 294

later.
The next speaker is speaker number 24.
Speaker number 24, your audio should be connected now. Please introduce yourself. Remember to state your name and any organization you are representing for the record.
(No response.)
DR. MEYER: Speaker number 24, can you hear us?
(No response.)
DR. MEYER: Okay. Speaker number 24, we're having trouble hearing you, so we will move on to the next speaker and try and return to you later in the session.
The next speaker should be speaker 25.
Speakers 25, your audio should be connected. Will you please begin and introduce yourself? And state your name and any organization you're representing for the record.
(No response.)
DR. MEYER: Okay. Speaker 25 --
DR. GHEI: Yes. I'm Nita Ghei. If I can

Page 295

have my slides, please?
Good afternoon. Thank you for the opportunity to participate in this workshop. I am Dr. Nita Ghei. I'm the director of research of headsUP Migraine, and I have no conflicts to disclose.
The main points I would like to make today are, first, the current use of MME conflates pain with disease, and it ignores the vast array of diseases and conditions that actually cause chronic pain. The use of MME by law enforcement that limits overdose deaths by tracking medical users and the physicians is destined to fail because the vast majority of overdose deaths is polypharmacy and associated with street drugs. Medically fragile patients and the physicians are the collateral damage of this misapplication of the MME.
The MME was designed for titration of dose for individual patients. The MME takes into account the wide variations of patients, the level of pain, response to medication, weight, and so

Page 296

forth. Ethically, MME should be used to determine the optimal outcome and care plan for the patient.
Instead, far too many agencies have grabbed on the CDC's 2016 guideline as hard rules. 90 MME, and even 50, have become the magic numbers. The CDC's judgment replaces that of the physician. Worse, with law enforcement tracking opioid prescriptions using MME and the threat of active forfeiture always present, it's safer for physicians to either taper to 90, or even 50, or simply decline to write prescriptions for opioids altogether.
Millions of sick Americans with chronic and progressive diseases have been medically abandoned. For a year, I was one of the abandoned, too. The current use of MME-treating physicians to treat patients is identical to the detriment. Different diseases and conditions all should be factors in determining a treatment plan. A universal 90 or 50 MME severely limits the physician's ability to do so.
Worse, however, is law enforcement state

Page 297

agencies tracking physicians by MME without context. Certain kinds of physicians will write more opioid prescriptions. Relying on MME by law enforcement fails to account for this. The resulting rates can disrupt care for thousands of patients.

The variance in opioids is conflation. The vast majority of overdose deaths are the result of alcohol and polypharmacy, mostly street drugs. Overdose deaths have increased even as opioid prescription numbers have fallen steadily since 2012. The actual numbers of patients who have prescription who overdose are very low, about 4 [indiscernible] percent in North Carolina to just over 1 percent in Massachusetts.

Pain patients are not the population where the bulk of overdoses are occurring. There's no evidence using MME to persecute treating physicians and pain patients will significantly reduce overdose deaths. Widening naloxone availability would be far more effective. Pain patients and the physicians are collateral damage in the opioid

Page 298

crisis. Returning MME to scientific evidenced-backed growth [indiscernible] would be a step in the right direction. Thank you.

DR. MEYER: Thank you very much, speaker number 25.

We are going to try and go back to speaker number 23.

Ms. Stewart, are you able to speak so we can make sure we can hear you?

MS. STEWART: I believe so. I think I figured it out this time.

DR. MEYER: Ah. We can hear you. Great. Okay. Please go ahead and introduce yourself. Remember to state your name and any organization you are representing for the record.

MS. STEWART: Alright. Thank you. My name is Tamera Stewart. I'm the national policy director for the P3 Alliance. We calculate that 21 to 26 percent of the American population would not be expected to respond, quote, "normally" to doses that are being incorrectly interpreted as limits in the CDC guideline, based solely on

Page 299

genetic makeup.

No other part of our government would knowingly regulate or discriminate against a quarter of Americans based on their DNA. We do not allow employers or insurance companies to treat customers differently based on genetic information, yet this is exactly what's happening in medicine.

Just this morning, Dr. Hayden [ph] spoke on pharmacogenomics and mentioned the populations from around the world have expected variations in specific CYP activities. My calculations on the population, excluded by the CDC guideline, were based on that same concept, extrapolated using the known percent of estimated frequency in each variant within each ethnic population in the U.S.

We all know that tolerance, health of organs, comorbidities, et cetera, all impact efficacy and the safety of pain medications. The P3 Alliance feels that any guideline or given definition of MME that doesn't account for these and other factors is falling short and even risks stepping into discriminatory medicine.

Page 300

No matter who sets that normal dose or how it's calculated, because of known variations, it's impossible to account for everyone. If recent reductions in prescribing were a valid solution and deserved to be celebrated as they are, many of the patients who were cut off or tapered to ineffective doses wouldn't still be suffering or further destabilizing.

None of today's presentations focused on reductions and prescribing mentioned tracking the patient outcomes. How are the veterans actually doing? When we speak to large groups of vets, their interpretation on how they're doing is considerably different.

It's obvious that desired positive outcome metrics are not universal, but it seems few ever include what the patient really views as important. It's common, even though we claim the entirety of medicine is about treating patients individually. If inflexible guidelines, algorithms, and definitions based on an imperfect concept of MME are continued to be allowed, we'd like to ask the

Page 301

FDA to require tracking to learn if the given MME, or how it's being defined, is effective according to positive outcome metrics that actually matter to the patients.

Knowing that as many as 21 to 26 percent of Americans don't respond, quote, "normally," any official action taken by government agencies or state or local governments attempting to standardize anything with opioids must include a way to ensure that that variability is being accounted for. Thank you.

DR. MEYER: Thank you very much, speaker number 23.

Let's try speaker number 24 again. Can you hear us?

MS. FUQUA: I can hear you. Can you hear me?

DR. MEYER: Yes. You sound great.

MS. FUQUA: Okay. Great.

DR. MEYER: Your audio's connected, so you can go ahead and state your name and any organization you're representing for the record,

Page 302

and start your presentation. Thank you.

MS. FUQUA: My name is Anne Fuqua. I'm a member of the National Pain Advocacy Center's Community Advisory Council and assist with CSI:OPIOIDS, a pilot study that seeks to examine suicides in patients with chronic pain.

The morphine milligram equivalent was originally intended to serve as a means to roughly compare the effects of various members of the opioid class of medications to what was mentioned as the gold standard, opioid, morphine. MME was never intended to function as an indicator of quality care, [indiscernible – audio distorted], or a threshold [indiscernible]. Yet, MME is now commonly used in each of these situations, as well as numerous others, though it was never intended.

I am so grateful for the many professionals who have spoken so forcefully on this subject today. Morphine milligram equivalents has been [indiscernible] CDC guideline. The impact on patients have been both widespread and [indiscernible]. As a chronic pain patient with

Page 303

multiple CYP cytochrome 450 [indiscernible], I've experienced many of the problematic issues related to MME described by Drs. McPherson and Fudin.

Doses that would be both unnecessary [indiscernible] allow me to enjoy a good quality of life. My overall health has dramatically improved. I live in a city with some of the finest healthcare providers in the nation, yet I must fly across the country every three months just to get medical care and maintain the quality of life I now have.

[Indiscernible] of medical care is an ever present concern that should not even be a consideration in the 21st century in the United States of America. An MME above 90 in a patient who is stable and functioning well without considerable risk is somewhat like a false alarm. This can lead to involuntary tapers, which elevates the risk to patients, and in fact results in actual harm, even death.

A lower MME can provide a false sense of security even when [indiscernible]. An example of this could be a physician that prescribed codeine

Page 304

[indiscernible] opioids. However, he is unaware that his patient has a CYP450 2D6. Also, providers should be able to focus on their patients, their pain, and the manner in which their pain impacts the patient's ability to function. In the current policy environment, having to focus on MME [indiscernible] and the real issues that the patient is experiencing. Thank you.

DR. MEYER: Thanks very much, speaker 24.

Speakers 26 and 27 did not confirm their participation for today, so we will now go to speaker number 28.

MS. STIESS: Hello? Can you hear me?

DR. MEYER: Yes. Your audio is connected. We can hear you. So ahead and introduce yourself. State your name and any organization you are representing for the record.

MS. STIESS: Hello. My name is Samantha Stiess. I am representing myself today. I have no financial issues or [indiscernible – audio distorted].

Thank you for letting me speak. My voice is

Page 305

quiet, but it will be heard today. I've been suffering from eight chronic pain diseases, including RSD, tardive dyskinesia, polycystic ovarian syndrome, [indiscernible] cultures, chronic migraine, depression, and anxiety since I was 15 years old. I'm now 35. I don't remember one day that I was well. I've tried everything from [indiscernible] naturally: physical therapy, cortisone shots; trigger blocks, and [indiscernible], and I started to get one more block at 16.

Once you've been diagnosed with a lifelong chronic pain illness, you don't get narcotics and a pat on your back. You try every step possible, but you don't have them until you have no options left.

At 21, I've had two botched spinal cord stimulators that made my disease spread throughout my entire body. Something that was promised to give my life back took it away even more, caused permanent harm and damage, and it wasn't a narcotic pain medication.

At 28, I found my [indiscernible] dose of

Page 306

medication and my third spinal cord stimulator to keep me looking like a semi-normal human being. I was able to do everything with my husband, even lose 75 pounds because, yes, it took 12 to 15 years to find that perfect dose.

I also get violently ill from [indiscernible] narcotic pain medication, because you have to realize, no one chooses this. All the NSAIDs, biopsies, and Celebrexes led me to a stomach ulcer at 16 years old, and I never fully got better at 35.

I never failed a drug test. I did everything I was told, even to recently getting a pain pump because doctors are too scared to write an oral prescription, but have absolutely no issue cutting your body open and putting other implants in you at all for the sake of not losing their license. With no extra pain medication after surgery, if the pump doesn't work, they will still take your medication away and go, "Tough luck." How crazy does that sound?

Five years ago, my life was taken away from

Page 307

bulky agendas and misinformation by the CDC, PROP, and the DEA. I lost my best pain management doctor who gave me my life back and my pain medication to let me function like a normal human being. If you know what it's like to lose your life over and over again, you would understand exactly how we feel.

I purposely [indiscernible] individuals with absolutely no science backup [indiscernible]. PROP and the CDC are exactly the boy who cried wolf. There isn't an opioid crisis, however, there is an illegal fentanyl and heroin crisis from drug addicts, not chronic pain sufferers, in our country because all agencies want to pigeonhole us together and not realize our care. Bad drug addicts will always find a way to get high and make all of you look like a bunch of fools.

Chronic pain patients just want their life back. With regulated narcotic pain medication we got from our pharmacies, we never got high off medication. We just want to live a life that was semi-normal for us, and we can't even have that now.

Page 308

Can you tell me you guys know the difference between a drug addict and a chronic pain patient after five years that you tortured and that you've bestowed upon us? This is a human rights violation. We know it. We deserve better than this hand that we've dealt with. We need to go after PROP and the CDC and the DEA for immoral drug [indiscernible] human rights violation.

I lost my life, but I'm speaking out on the people who can't take one more day of their pain, and under their advice [indiscernible] narcotic pain medication with. I've been on [indiscernible] for five years. I have now an 11-month-old baby that I have to take care of. My blood pressure is going through the roof because my pain is not controlled or stabilized anymore.

My 75 pounds I once lost is piling back up. My high-risk pregnancy, I almost didn't make it out alive. I hemorrhaged. After my C-section, I needed two blood transfusions. I still wasn't given anything extra but ibuprofen, and that was blood. Smart, right?

Page 309

I see the number of overdoses especially increasing since COVID. Pharmaceuticals have been decreasing heavily for five years since PROP, and its doctors who aren't pain management doctors at all, and have no business deciding our fate, and who went and destroyed the chronic pain patient's way of life and not help the drug addicts' life at all, mentally or physically.

Why do we hear one side of the story from the media? What are you going to do to fix this? Why don't you realize it's illegal fentanyl and heroin on the street killing drug addicts, not chronic pain patients that are committing suicide rather than going out on the street?

Can all the big corrupted agencies know the difference between chronic pain patients, who are dropping like flies because you took our only lifeline away, but absolutely --

DR. MEYER: Speaker 28?

MS. STIESS: Yes?

DR. MEYER: I'm sorry. Your time is up. Can you please just wrap up your comments? Thank

Page 310

you.

MS. STIESS: Yes. Kale, yoga, and Tylenol, and prayers aren't going to do anything for us, who've already tried everything possible to stop our pain. Thank you so much for your time.

DR. MEYER: Thanks very much, speaker 28.

Speaker numbers 29 and 30 were unable to confirm their participation for today, so we will now move to speaker number 31.

Speaker number 31, your audio should be connected. Please begin and introduce yourself, and remember to state your name and any organization you're representing for the record.

MS. CORLEY: Hi. My name is Donna Corley, and I'm the director of ASAP or Arachnoiditis Society for Awareness and Prevention. Thank you on behalf of millions of chronic pain patients living with rare, debilitating diseases such as adhesive arachnoiditis, Tarlov cyst disease, EDS, eRPS, just to name a few.

When the 2016 CDC guideline were implemented, not one part of it was considered for

Page 311

patients who suffered with rare disease or who have metabolic issues such as being a poor or rapid metabolizer of opioid medications with regards to the MME dosage restriction. This issue was brought to the CDC's attention many times by myself and others to no avail.

As an advocate, I always believed there was equality for everyone, regardless of race, sex, religion, or even social status. Sadly, this has not been the case for those of us who suffer with these intractable pain diseases. In fact, we have received just the opposite and been ostracized, stigmatized, traumatized, and left by the wayside without care of any kind by physicians who were too afraid of state and federal regulations to offer or continue treatment that many patients have been receiving successfully prior to the implemented CDC guideline.

What has happened to pain patients since 2016 has been nothing short of tragic: forced tapering of their medications; forced withdrawal; loss of their stable medications; loss of their

Page 312

physicians; loss of jobs and livelihood, causing many to seek disability and Medicaid; uncontrolled pain, causing many to seek suicide as the only viable solution left to them to end their torturous agony, all thanks due to the MME dosage threshold based on faulty science, lacking any sound consensus among numerous experts, including the CDC authors themselves and the -- [inaudible – audio lost].

DR. MEYER: Speaker 31, I lost you.

(No response.)

DR. MEYER: Can you try and say something again?

(No response.)

DR. MEYER: Okay. I think we're having some technical difficulties. Just give us a minute to try and work it out.

(Pause.)

DR. MEYER: Okay. Just bear with us. We're having some technical difficulties. We want to give the speaker time to call back in. Thank you.

MS. CORLEY: Hello?

DR. MEYER: Hi. Is that Donna?
MS. CORLEY: Hi -- AMA went on to say [inaudible – audio gap] -- I'm echoing.
DR. MEYER: Hi. I just want to remind people to mute their phones, And if you're listening through computer audio while you're speaking, make sure your computer audio is turned down all the way.
Okay. Try again.
MS. CORLEY: The truth of the matter is that the MME threshold remains a hard policy by many health insurers, pharmacies, and state medical boards. The AMA strongly urged the CDC to add language to the revised CDC guideline, urging those entities to rescind these policies given the absence of data to suggest a relationship between the arbitrary threshold and improved patient outcomes, as well as the harms done to patients as a result of inappropriate tapering or denial of care.
The FDA has the opportunity to undo the massive harms of millions of pain patients all



across the country. On behalf of all those who couldn't be here to speak for themselves today, we're begging you to do the right thing and stop this devastation. Thank you.
DR. MEYER: Thank you very much, speaker 31.
Speakers 32 through 35 were not able to join today or did not confirm their participation, so this is the end of the public comment session.
The public comment session of the workshop is now concluded. Information on how to submit to the docket for any remaining comments are being shown on the screen right now. We understand that the virtual meeting format may have made it challenging for some people to participate in the public comment session today, but we really truly want to hear from you. If you have any additional comments that you are unable to submit or to speak about today, please submit them to the docket. If you have problems with submitting to the docket, reach out to us so that we can help you. We truly do consider these submissions carefully along with the rest of the meeting materials.



I want to sincerely thank all of the public comment session speakers for sharing your experiences and your insights on this topic. The comments we have heard today will be carefully considered by the FDA and the panel in the discussion tomorrow.
I'm now going to turn the meeting back over to Dr. Chai for any closing comments.

Closing Remarks – Grace Chai

DR. CHAI: Thank you, Dr. Meyer.
Before we adjourn, I'd also like to thank all the meeting participants today, from the speakers for their excellent presentations, as well as the panelists for questions, and a very special thank you to those who spoke during the public comment session. We hear you. As Dr. Meyer said, patients and public health are our priority and reinforce why we are meeting to discuss the science.
As Dr. Meyer stated, the public docket, as cited in the Federal Register notice, will be open through August 9, 2021 for your feedback. You are



encouraged to post further comments there. And as a gentle reminder, meeting materials, including the agenda for day 2 and the panel discussion questions, are posted on the meeting website.
Thank you again to all participants and to the audience for attending today. We look forward to reconvening tomorrow at 9 a.m. Eastern Daylight Time to continue this important scientific workshop. We will now adjourn the meeting. Thank you for your participation.
(Whereupon, at 4:21 p.m., the meeting was adjourned.)

## C

## D

## E

## F

## G

## H

## I

## M

## N

## O

## P

## Q



## R

## S

## T

## U