

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

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*June 7, 2021*

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

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<p>1 FOOD AND DRUG ADMINISTRATION</p> <p>2</p> <p>3</p> <p>4 Center for Drug Evaluation and Research (CDER)</p> <p>5</p> <p>6 Public Virtual Scientific Workshop</p> <p>7</p> <p>8 Morphine Milligram Equivalents</p> <p>9 Current Applications and Knowledge Gaps,</p> <p>10 Research Opportunities, and Future Directions</p> <p>11</p> <p>12</p> <p>13 Day 1</p> <p>14</p> <p>15</p> <p>16 Monday, June 7, 2021</p> <p>17 9:00 a.m. to 4:21 p.m.</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p>	<p>1 Sandra Comer, PhD</p> <p>2 Professor of Neurobiology</p> <p>3 Department of Psychiatry at Columbia University</p> <p>4 Research Scientist VI</p> <p>5 New York State Psychiatric Institute</p> <p>6</p> <p>7 Penney Cowan</p> <p>8 Founder, CEO American Chronic Pain Association</p> <p>9</p> <p>10 Francesca Cunningham, PharmD</p> <p>11 Department of Veterans Affairs</p> <p>12</p> <p>13 Nabarun Dasgupta, MPH, PhD</p> <p>14 University of North Carolina at Chapel Hill</p> <p>15 Departmental Affiliation</p> <p>16 Gillings School of Global Public Health and</p> <p>17 Injury Prevention Research Center</p> <p>18</p> <p>19 Thomas Emmendorfer, PharmD</p> <p>20 Department of Veterans Affairs</p> <p>21</p> <p>22</p>
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<p>1 Meeting Roster</p> <p>2 Shanna Babalonis, PhD</p> <p>3 Assistant Professor</p> <p>4 Center on Drug and Alcohol Research</p> <p>5 College of Medicine, University of Kentucky</p> <p>6</p> <p>7 Jeffrey J. Bettinger, PharmD</p> <p>8 Clinical Pharmacist Specialist, Pain Management</p> <p>9 Saratoga Hospital Medical Group</p> <p>10</p> <p>11 Patrizia Cavazzoni, MD</p> <p>12 Director - Center for Drug Evaluation and Research</p> <p>13 FDA</p> <p>14</p> <p>15 Grace Chai, PharmD</p> <p>16 Associate Director for Special Initiatives</p> <p>17 Office of Surveillance and Epidemiology (OSE)</p> <p>18 CDER, FDA</p> <p>19</p> <p>20 Brooke Chidgey, MD</p> <p>21 Division Chief of Pain Management</p> <p>22 University of North Carolina, Chapel Hill</p>	<p>1 Perry G. Fine, MD</p> <p>2 Professor of Anesthesiology</p> <p>3 University of Utah</p> <p>4 Salt Lake City</p> <p>5</p> <p>6 Jeffrey Fudin, PharmD, FCCP, FASHP, FFSMB</p> <p>7 Albany College of Pharmacy and Health Sciences</p> <p>8 Albany NY</p> <p>9 Western New England University College of Pharmacy</p> <p>10 Springfield MA</p> <p>11 Stratton VA Medical Center</p> <p>12 Albany NY</p> <p>13 Remitigate Therapeutics</p> <p>14 Delmar NY</p> <p>15</p> <p>16 David J. McCann, PhD</p> <p>17 Associate Director of the Division of</p> <p>18 Therapeutics and Medical Consequences</p> <p>19 National Institute on Drug Abuse (NIDA)</p> <p>20 NIDA, National Institutes of Health (NIH)</p> <p>21</p> <p>22</p>

Page 5	<p>1 Mary Lynn McPherson, PharmD, MA, MDE, BCPS                  2 Professor and Executive Director                  3 Advanced Post-Graduate Education in Palliative Care                  4 Executive Program Director                  5 Online Master of Science and Graduate Certificate                  6 Program in Palliative Care                  7 Department of Pharmacy Practice and Science                  8 University of Maryland School of Pharmacy                  9                  10 R. Daniel Mellon, PhD                  11 Division of Pharmacology/Toxicology for                  12 Neuroscience                  13 Office of Neuroscience (ON)                  14 Office of New Drugs (OND)                  15 CDER, FDA                  16                  17 Tamra Meyer, PhD MPH                  18 Team Lead, Nonmedical Use Team #1                  19 Division of Epidemiology II                  20 OSE, CDER, FDA                  21                  22</p>	Page 7	<p>1 Chad J. Reissig, PhD                  2 Behavioral Pharmacologist                  3 Controlled Substance Staff                  4 Office of the Center Director (OCD)                  5 CDER, FDA                  6                  7 Friedhelm Sandbrink, MD                  8 National Program Director for Pain Management,                  9 Opioid Safety and PDMP (PMOP)                  10 Specialty Care Services                  11 Veterans Health Administration                  12 Director Pain Management                  13 Department of Neurology                  14 Washington DC VA Medical Center                  15                  16 Judy A. Staffa, PhD, RPh                  17 Associate Director for Public Health Initiatives                  18 OSE, CDER, FDA                  19                  20                  21                  22</p>
Page 6	<p>1 Maria Luisa Molinari, MD                  2 Senior Clinical Assessor at the Medicine and                  3 Healthcare Products Regulatory Agency (MHRA)                  4 PGDip in Drug Development Science                  5 King's College London                  6                  7 Jennifer Nadel, MD                  8 Medical Officer                  9 Division of Anesthesiology, Addiction Medicine, and                  10 Pain Medicine                  11 ON, OND                  12 CDER, FDA                  13                  14 Mary Therese O'Donnell MD, MPH                  15 Medical Reviewer                  16 Division of Anesthesiology, Addiction Medicine and                  17 Pain Medicine                  18 ON, OND, CDER, FDA                  19                  20 Justin Pittaway-Hay, PhD                  21 Medicine and Healthcare Products                  22 Regulatory Agency (MHRA)</p>	Page 8	<p>1 Donna A. Volpe, PhD                  2 Division of Applied Regulatory Science                  3 Office of Clinical Pharmacology (OCP)                  4 CDER, FDA                  5                  6 David A. White, PhD                  7 Director of National Institute on Drug Abuse's                  8 Addiction Treatment Discovery Program                  9 Division of Therapeutics and Medical Consequences                  10 NIDA, NIH                  11                  12 Corinne Woods, RPh, MPH                  13 Team Lead, Drug Utilization Team                  14 OSE, CDER, FDA                  15                  16 Kun Zhang, PhD                  17 Health Scientist                  18 Division of Overdose Prevention                  19 National Center for Injury Prevention and Control                  20 Centers for Disease Control and Prevention (CDC)                  21                  22</p>

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P R O C E E D I N G S

(9:00 a.m.)

1 Welcome and Panelists Introductions

2

3 DR. CHAI: Good morning and welcome. Thank

4 you for joining us virtually for this Public.

5 Scientific Workshop on Morphine Milligram

6 Equivalents: Current Applications and Knowledge

7 Gaps, Research Opportunities, and Future

8 Directions. I would first like to remind everyone

9 to please mute your line when you are not speaking.

10 My name is Grace Chai, and I am the

11 associate director for Special Initiatives in the

12 Office of Surveillance and Epidemiology under the

13 Center of Drug Evaluation and Research here at FDA,

14 and I will be chairing this meeting.

15 First, I would like to start with a few

16 housekeeping details. Meeting materials, including

17 the agenda, list of speakers, and panelists' names

18 and the disclosures, are available online, posted

19 on the meeting website.

20 Please note, the meeting recording and

21 slides are expected to post at a later date,

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

7 Today, the first break will occur around  
8 11 a.m., and lunch is scheduled for approximately  
9 12:25 p.m. today. Please plan accordingly.

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

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

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

22 DR. CHAI: Thank you.

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1 Dr. Bettinger?

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

7 DR. CHAI: Thank you.

8 Dr. Chidgey?

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

13 DR. CHAI: Thank you.

14 Dr. Comer?

15 (No response.)

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

18 (No response.)

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

20 Ms. Penney Cowan?

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

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1 Chronic Pain Association.

2 DR. CHAI: Thank you.

3 Dr. Cunningham?

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

9 DR. CHAI: Dr. Dasgupta?

10 (No response.)

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

13 (No response.)

14 DR. CHAI: We'll come back.  
15 Dr. Emmendorfer?

16 (No response.)

17 DR. CHAI: Dr. Fine?

18 (No response.)

19 DR. CHAI: Dr. Fudin?

20 DR. FUDIN: Hello?

21 DR. CHAI: Oh, hi. Could you introduce --  
22 DR. FUDIN: This is Dr. Fudin.

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1 DR. CHAI: Thank you.

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

9 DR. CHAI: Thank you, Dr. Fudin.

10 Dr. McCann?

11 (No response.)

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

14 Dr. McPherson?

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

20 DR. CHAI: Thank you.

21 Dr. Molinari?

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

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1 Molinari. I'm a clinical medical assessor from the  
2 MHRA in the UK.  
3 DR. CHAI: Thank you.  
4 Dr. Pittaway-Hay?  
5 DR. PITTAWAY-HAY: Hello. It's Justin  
6 Pittaway-Hay. I'm a PK assessor at the MHRA.  
7 DR. CHAI: Thank you.  
8 Dr. Sandbrink?  
9 DR. SANDBRINK: Good morning. I'm the  
10 national program director for pain management,  
11 opioid safety, and prescription drug monitoring  
12 programs in the Veterans Health Administration.  
13 I'm the director for pain management at the  
14 Washington, D.C. VA Medical Center, and I have  
15 academic affiliation with the Uniformed Services  
16 University in Bethesda and George Washington  
17 University in Washington D.C.  
18 DR. CHAI: Thank you.  
19 Dr. White?  
20 DR. WHITE: Good morning. My name is David  
21 White. I am the director of the Addiction  
22 Treatment Discovery Program at NIDA, which is part

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

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

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

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1 Evaluation and Research at the FDA.  
2 DR. CHAI: Thank you.  
3 Dr. Reissig?  
4 DR. REISSIG: Good morning. My name is Chad  
5 Reissig, and I'm a pharmacologist with the  
6 controlled substance staff at FDA.  
7 DR. CHAI: Thank you.  
8 Dr. Staffa?  
9 DR. STAFFA: Good morning. I'm Judy Staffa.  
10 I'm the associate director for Public Health  
11 Initiatives in the Office of Surveillance and  
12 Epidemiology in CDER at FDA.  
13 DR. CHAI: Thank you.  
14 Dr. Volpe?  
15 DR. VOLPE: Good morning. My name is Donna  
16 Volpe. I'm a researcher in the Division of Applied  
17 Regulatory Science in CDER, in the FDA.  
18 DR. CHAI: Corinne Woods?  
19 MS. WOODS: Good morning. My name is  
20 Corinne Woods. I'm one of the team leads on the  
21 Drug Utilization Team in the Office of Surveillance  
22 and Epidemiology at CDER, at FDA.

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

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1 We have scheduled clarifying question  
2 sessions following groups of presentations. We  
3 encourage all panelists to jot down any clarifying  
4 questions you may have for presenters. Please take  
5 note of the times for clarifying question sessions  
6 on the agenda.  
7 Due to scheduling conflicts, a few  
8 participants will not be able to join us tomorrow  
9 on day 2. We ask for any clarifying questions for  
10 Dr. Emmendorfer, Dr. Cunningham, Dr. Fudin,  
11 Dr. Molinari, and Dr. Pittaway-Hay to be asked  
12 today for their presentations. We look forward to  
13 a productive meeting.  
14 To kick off this two-day scientific  
15 workshop, we will now hear opening remarks from  
16 Dr. Patrizia Cavazzoni, director of the Center for  
17 Drug Evaluation and Research at the U.S. Food and  
18 Drug Administration.  
19 Thank you, Dr. Cavazzoni.  
20 (No response.)  
21 DR. CHAI: Are you able to unmute your line?  
22 DR. CAVAZZONI: Yes, I am. Can you hear me

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1 ok?  
2 DR. CHAI: Yes. Thank you.  
3 DR. CAVAZZONI: Very good. Very good.  
4 Opening Remarks – Patrizia Cavazzoni  
5 DR. CAVAZZONI: Good morning, everyone, and  
6 welcome to our public workshop. It is an honor to  
7 be with you today. A special thank you to the  
8 attendees and organizers of this workshop for  
9 coming together, especially in light of the  
10 extraordinary challenges and hardships we have all  
11 faced this past year.  
12 Indeed, this is a critical time in our  
13 nation's history. As the COVID-19 pandemic  
14 progressed, we saw drug overdose deaths reach a  
15 record high, and the opioid crisis continue to  
16 devastate families and communities across the  
17 Nation.  
18 Throughout it all, the opioid crisis has  
19 remained an urgent public health priority for the  
20 FDA. Using all available evidence and tools at our  
21 disposal, the agency is committed to reversing this  
22 trend and ensure safe prescribing of all

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

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

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

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



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1 panelists for their time and efforts in preparation  
2 for this meeting, and would especially like to  
3 acknowledge and thank all those that have devoted  
4 months of hard work to prepare for this two-day  
5 virtual scientific workshop to inform an advance on  
6 the science underlying morphine milligram  
7 equivalents or MMEs.  
8 First, I'd like to start with what is an  
9 MME. Here's one definition, courtesy of our CDC  
10 colleagues. MME is defined as the amount of  
11 milligrams of morphine an opioid dose is equal to  
12 when prescribed. Calculating MME accounts for  
13 differences in opioid drug type and strength and  
14 has been used for years in patient care, such as to  
15 inform on starting dose when converting from one  
16 opioid to another.  
17 More recently, MMEs or other similar terms  
18 are increasingly being used to indicate abuse and  
19 overdose potential and to set thresholds for  
20 prescribing and dispensing of opioid analgesics.  
21 To set the stage for this two-day workshop,  
22 here are the purpose and goals of the scientific

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1 meeting. The purpose of this meeting is to bring  
2 experts and stakeholders together to discuss the  
3 scientific basis underlying morphine milligram  
4 equivalents, which are widely used as metrics in  
5 multiple areas throughout the healthcare system.  
6 Speakers over the next two days will present  
7 on a range of topics regarding the science  
8 underlying the space which we are referring to as  
9 MMEs. Presentations include a discussion of the  
10 uncertainties and complexities, not only in the MME  
11 conversion factors themselves but in the  
12 calculation and application of MMEs, as well as the  
13 use of MMEs as risk predictors for overdose,  
14 non-medical use, or the development of opioid-use  
15 disorder.  
16 Tomorrow afternoon will be devoted to panel  
17 discussions when our speakers and additional  
18 panelists will discuss key topics on the state of  
19 the science and inform on a future research agenda.  
20 This workshop is to highlight the science and  
21 encourage all stakeholders, including government  
22 agencies, academia, and others, to join in

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1 contributing to advancing the science in this  
2 space.  
3 Ultimately, patients and public health  
4 continue to be our priority. We will start the day  
5 by hearing how science impacts patients,  
6 reinforcing the need for a better understanding and  
7 advancement of the science in this space.  
8 Today, we will hear the patient's  
9 perspective both from an invited speaker, as well  
10 as during the public comment session. To help  
11 facilitate a productive meeting to meet these  
12 goals, I would also like to clarify what we will  
13 not focus on in this two-day meeting.  
14 We recognize that the workshop's discussion  
15 of the science may have implications on specific  
16 applications of MMEs, however, discussion of  
17 specific regulatory actions, policies, and  
18 applications of MMEs is not the focus. Our goals  
19 are for a better collective understanding and  
20 future collaborative advancement of the science  
21 underlying MMEs.  
22 Presentations today will provide more depth

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1 into these topics, including the history and  
2 scientific basis of MMEs, both what is known as  
3 well as gaps in the science, as well as the varying  
4 uses of MMEs across different applications.  
5 Presentations will also show the existence of  
6 multiple resources, including reference tables,  
7 guidelines, online calculators, and other tools  
8 that may use or cite different MME factors.  
9 Presentations will also highlight the challenges  
10 regarding individual patient and drug  
11 characteristics that may influence the use and  
12 calculation of MMEs.  
13 Recent public health focus includes the use  
14 of MMEs as a measure of dose often in tools to  
15 address the opioid crisis. Some of this interest  
16 in MMEs may have come from epidemiologic studies  
17 showing a convincing association between increasing  
18 daily dose of opioid analgesics and increasing risk  
19 of overdose. These studies generally used daily  
20 MME thresholds of 50 or 90 MMEs to assess risk.  
21 Studies have also examined the association between  
22 daily dose and adverse outcomes, but it's important

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1 to note that these studies are challenging to  
2 conduct and causality is unclear.  
3       Given the complexity about MMEs and how they  
4 are used, I will take some time to walk through  
5 this influence diagram we created to help  
6 illustrate the complexity, as well as to structure  
7 some of the topics and discussions you'll see and  
8 hear over the next two days.  
9       This is not a comprehensive model, nor was  
10 it designed to be. The variables represented here  
11 were drafted to give the system view of many moving  
12 parts that should not be considered in isolation.  
13 While we do not have complete information on many  
14 aspects of this diagram, the diagram shows the most  
15 common stakeholders that may use them and the  
16 potential resulting influences. The arrows  
17 demonstrate a believed relationship that is a  
18 possible influence of one factor on another that  
19 connects the uses to potential outcomes.  
20       It all starts with the science, what is  
21 known, as well as emerging research, which inform  
22 the space of MMEs or opioid comparisons. MME

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1 factors are often used in various algorithms to  
2 calculate MME per day or other measures. In  
3 addition to varying patient and drug  
4 characteristics that influence the use of MMEs, the  
5 existence of multiple online calculators and tools,  
6 as well as variability and calculations amongst  
7 healthcare providers themselves, complicate these  
8 factors.  
9       Many of our presenters will be going in  
10 depth into these topics. These areas in this blue  
11 box comprise the main focus of our scientific  
12 workshop over these two days, however, the  
13 application and use of MMEs is critical in the  
14 consideration of the science and how science  
15 informs the application of MMEs.  
16       Uses of MMEs have expanded into varied uses  
17 across clinical practice in prescribing, and  
18 dispensing, as well as in reimbursement and  
19 regulation at various levels and in research, both  
20 in the U.S. and globally. In addition to our  
21 US-based experts and stakeholders, we are also  
22 fortunate to have our colleagues from the United

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1 Kingdom joining us today to provide insight from  
2 their perspective.  
3       As stated earlier, our common priority is  
4 patients and public health and how science impacts  
5 patients, highlighting the importance of  
6 understanding the science. The opioid crisis is  
7 highly complex. This diagram illustrates some of  
8 the complexities, as well as the potential  
9 wide-ranging influences of MMEs.  
10       As Dr. Cavazzoni spoke about, the opioid  
11 crisis continues to be a critical public health  
12 priority. We understand and recognize the need and  
13 desire to discuss much more than the goals we have  
14 outlined today. We also recognize discussions may  
15 have future implications on the application of  
16 MMEs. However, as stated earlier, we will not  
17 discuss changes to specific policies or seek to  
18 undermine specific uses of MMEs.  
19       Enhancing evidence-based approaches by  
20 collectively leaning in to inform and develop the  
21 science where it is needed is what we are here to  
22 facilitate today, with the goals of better

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1 equipping all stakeholders with a more thorough  
2 understanding of the science underlying MMEs.  
3       Over the next two days, you will hear from  
4 many experts and stakeholders in this field.  
5 Meeting materials are available online, including  
6 the agenda with the order of presentations, titles,  
7 and speakers. Tomorrow, we will hold the panel  
8 discussions. Please take note of the panel  
9 discussion questions to be discussed, also  
10 available online.  
11       For your convenience and reference, here is  
12 the agenda for the next two days. I'd also like to  
13 orient you to the panel discussion questions that  
14 we will be discussing tomorrow for your reference,  
15 as well as to prepare you for tomorrow.  
16       I'd like to thank you for your time and  
17 attention. Next, we will hear from Ms. Penney  
18 Cowan, founder and CEO of the American Chronic Pain  
19 Association, on a patient's perspective and how  
20 science impacts real-life experiences. Thank you.  
21       Presentation – Penney Cowan  
22       MS. COWAN: Thank you, and good morning,

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1 everyone. Again, my name is Penney Cowan. I'm the  
2 founder and CEO of the American Chronic Pain  
3 Association.  
4 Before I start -- I'm going to talk about  
5 the impact of science on real-life  
6 experience -- just a little background into the  
7 American Chronic Pain Association. We've been  
8 around since 1980. We facilitate peer support  
9 groups and education for individuals with chronic  
10 pain and their families so that they can live more  
11 fully in spite of their pain, and to raise  
12 awareness among health care, policymakers,  
13 community, and the public at large about many  
14 issues of living with chronic pain.  
15 I want to start with the time line of where  
16 I have seen pain go over the last 40 years since  
17 I've been involved. In the late '70s, one of the  
18 things that really stood out -- and I had my own  
19 personal experience with it -- was pain management  
20 programs, the interdisciplinary or  
21 multidisciplinary pain programs that really started  
22 with the movement by John Bonica. All of these

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1 programs were very interactive. They provided all  
2 of the necessary skills, and support, and medical  
3 interventions that a person needed to really begin  
4 that journey from patient to person.  
5 So I was fortunate enough to spend time at  
6 the Cleveland Clinic at an inpatient program, which  
7 many of them were. As I graduated from the  
8 program, I realized that while they taught me how  
9 to live with my pain, they didn't take it away  
10 because there's always going to be some level of  
11 pain.  
12 To give you a background on where we're at,  
13 our goal of pain management is to improve quality  
14 of life and increase function while reducing one's  
15 sense of suffering. That's truly important.  
16 Nowhere does it say get rid of the pain. So people  
17 teach you how to live with pain, how to manage it,  
18 but it's up to that individual to continue to  
19 maintain their wellness over a long period of time.  
20 Thus, that's why I started the American  
21 Chronic Pain Association, for a variety of reasons.  
22 At one point as we got going, I would get an email

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1 from CARF, which is the Commission on the  
2 Accreditation of Rehabilitation Facilities, once a  
3 month giving me information about every  
4 CARF-accredited interdisciplinary/  
5 multidisciplinary pain management program in the  
6 country. And there were close to 2,000 of these,  
7 both inpatient and outpatient.  
8 Then in the late '80s, what I saw is a real  
9 shift in the way people were looking at managing  
10 pain. I think a lot of it had to do with the  
11 payers, because instead of reimbursing for the  
12 interdisciplinary/multidisciplinary pain management  
13 programs, they saw that the interventionalists, the  
14 TENS units, the intrathecal pumps, and the nerve  
15 blocks, were really just as effective and a lot  
16 more cost effective.  
17 So we saw a real cut back in the number and  
18 availability of pain management programs. The more  
19 the interventionists came along and push and took  
20 over pain management, it was deemed to be the  
21 accepted way.  
22 The whole time, from the time I entered,

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1 even through all the time with interventionists,  
2 one of the things that I kept hearing over and over  
3 again was that opioids were not the way to manage  
4 pain. Ed Covington was actually the director of  
5 the pain program when I went through it, and I can  
6 remember him saying, "If you take an opioid, a  
7 person with pain is going to have two problems.  
8 They're going to have pain and they're going to be  
9 addicted." So that sort of has stuck in my mind  
10 all this time.  
11 Then in the late '90s, here come people  
12 saying, "Oh, opioids are ok to take," and it was  
13 probably the most confusing thing. And it was  
14 really hard for me to accept because for so long it  
15 was like that wasn't the thing to do. We had to  
16 look at all the other components of pain management  
17 in order to help people manage their pain, but all  
18 of a sudden opioids were the thing to do.  
19 So here we are through the late '90s into  
20 the 2000s, and as we saw what happened, we had a  
21 huge influx of people taking opioids. We saw the  
22 media say -- and I can remember reading in the

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

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

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

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

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

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

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

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

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

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

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

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

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1 We surveyed a little more than a thousand people,  
2 and some of the things that we found were that  
3 56 percent had difficulty obtaining a prescription  
4 for their pain medication. These are people that  
5 had been taking it, functioning and working, and  
6 now 56 percent of them were having trouble.

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

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

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

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1 anymore." I mean, they put them right on their  
2 windows, right as you go into the office, into the  
3 door.  
4 I think one of the saddest things that we  
5 saw in this survey is that 47 percent of the  
6 respondents have contemplated suicide because they  
7 cannot find relief from their pain, and that's I  
8 think really, really sad. And when it comes to  
9 actually going to the pharmacy, 7 percent -- and I  
10 found this really interesting -- were asked to  
11 produce their complete medical record.  
12 I don't know about you, but I don't know  
13 anyone who carries around or even has access to  
14 their complete medical record to give to a  
15 pharmacist. Fifteen percent of them were simply  
16 refused to refill their prescription, and there was  
17 absolutely no reason given for why they're  
18 refusing.  
19 One of the problems is 18 percent of the  
20 pharmacists were concerned over the prescription.  
21 And what happened there is they would actually call  
22 the prescriber, the healthcare professional, and

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1 question them as to why they were giving this  
2 person high dose, so many of them. And providers,  
3 again, they don't have time for all of those calls,  
4 and why would you have to justify? Why would they,  
5 the person who is treating this person with pain,  
6 who knows them, who have been treating them, have  
7 to answer to the pharmacists when those kinds of  
8 calls came in? So again, one of the reasons they  
9 just stopped prescribing, it just wasn't worth the  
10 grief.  
11 So what did people do when they can't get  
12 their medications? They wanted and needed to live  
13 a normal life. And again, those are the calls we  
14 would get, people just wanting to get back to work,  
15 to be able to function, to provide for their  
16 family. But some of them just simply suffered.  
17 They suffered because they had to reduce it. Some  
18 hoarded their medications, taking a lot less than  
19 the amount that was prescribed for them so they  
20 wouldn't run out. They tried to space it over a  
21 long period of time.  
22 Many of them would go to the emergency room

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1 seeking relief, and they were sort of the ones that  
2 were called frequent flyers, where they would be  
3 refused after a while. And there were a few people  
4 that were actually arrested right out of the ED.  
5 Others self-medicated with alcohol and marijuana,  
6 and some were so desperate enough to turn to the  
7 street drugs, and I think that's really where we  
8 saw a lot of the problem and a lot of the  
9 heartbreak.  
10 Here are some of the quotes, and we had  
11 hundreds of these quotes in this survey. We always  
12 give people an opportunity to share their thoughts  
13 and feelings. These are quotes. I'm going to read  
14 them.  
15 "I started using illegal opioids after I was  
16 unable to get my medication."  
17 "I will have no choice but to commit suicide  
18 when I'm no longer able to travel out of state  
19 every three months to get my prescription."  
20 "I have fraudulently called in prescriptions  
21 and bought them off the street. The amount of  
22 guilt I feel is extraordinary. I have ruined my

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1 life."  
2 "I take meds to make me sleep as much as  
3 possible. I lie on the couch and watch TV and cry.  
4 I vomit a lot. And when I can't handle it anymore,  
5 I tell my wife to take me to the ER."  
6 This is one thing that people don't realize;  
7 it's not just the person with pain that's  
8 suffering. Family members are also directly  
9 impacted by this crisis and the impact it's having  
10 on that person with pain, and their ability not to  
11 work, and their inability to manage the pain.  
12 "I suffer in immense pain. This tears my  
13 family apart."  
14 "I stay in bed in agony, weeping, depressed,  
15 can't eat, can't work, sleep, or function. No  
16 quality of life. I feel lost, scared, and alone.  
17 Pain takes over my whole body and all aspects of my  
18 life." Those are just but a few of the many quotes  
19 we got.  
20 I want to step back and take a look at how  
21 did we get to this point. I think one of the  
22 interesting things is that we don't look at

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1 expectations. We don't look at the expectations of  
2 the person with pain or the healthcare  
3 professional. In other words, when a person goes  
4 to their healthcare provider, how often are they  
5 asked what's their goal of pain management?  
6 They're asked their symptoms, their pain scores,  
7 and all these other things. But has a provider  
8 really ever taken the time to say what really are  
9 your goals?  
10 There was one PCORI project that they  
11 actually did this. They did it with primary care,  
12 and it was extremely interesting because what I saw  
13 is that the providers thought that they're going to  
14 want to get rid of their pain. And that's what I  
15 think a lot of healthcare providers think, and  
16 that's what they've been trained to do, is to heal.  
17 You help people heal, get better, and go back to a  
18 normal life. That is their expectation.  
19 But a person with pain, what was really  
20 interesting and what we heard, people's expectation  
21 was they knew, because so many of them had been  
22 living with this for so long, that it wasn't going

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1 to go away, but they wanted to get back to their  
2 normal life. They wanted to be able to go fishing  
3 again, to hold their grandchild, to walk up the  
4 steps to their art studio, to drive a car.  
5 Expectations are very different. It would  
6 be great if physicians started out, or healthcare  
7 professionals started out, by asking people, "What  
8 is your goal of treatment?" and set that goal, and  
9 work for that, and understanding, and really work  
10 as that team.  
11 Payers don't reimburse for many of the  
12 treatments and therapies, and that's one of the  
13 problems. Even though providers may know, go to  
14 physical therapy, massage, acupuncture,  
15 biofeedback, stress management, counseling, any of  
16 those things, payers aren't reimbursing. And if  
17 people do get to go to physical therapy, they limit  
18 the number of sessions that they're allowed to  
19 have, and that's not useful.  
20 People with pain were tapered far too fast  
21 or simply cut off without any pain management  
22 interventions whatsoever, and this was really a big

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1 problem because so many people were just cut off;  
2 we won't prescribe anymore. They never thought  
3 about what is this person going to do.  
4 Just because they're not taking opioids  
5 doesn't mean they're not going to have pain. They  
6 still have pain. They still need to be able to  
7 manage that pain. It gets back to those kinds of  
8 quotes that we had, and the number of people who  
9 really thought about ending their life because of  
10 the pain, so it was really hard; or a lot of them  
11 because providers, unfortunately not all of them  
12 were trained in how to taper. A lot of them were  
13 tapered too fast, and it wasn't useful.  
14 Many of them, what they heard was just,  
15 "You're going to have to learn to live with it,"  
16 and that's something that all of us have heard  
17 living with pain, and this is something that I  
18 heard many times before I went to a pain management  
19 program. While I'm very creative and I really work  
20 hard at doing whatever I can to accomplish any task  
21 or resolve any problem, I could not figure out how  
22 to manage my pain, and I did look to healthcare

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1 providers.  
2 It's sort of like this problem. I mean,  
3 it's impossible. And that's what it looks like  
4 when you tell someone to learn to live with their  
5 pain; impossible, because if you asked me to solve  
6 this problem, I would have no clue what it is and  
7 how to do it. But if I started taking classes and  
8 took some in algebra and went up to plane geometry,  
9 calculus, trig, and maybe work my way up to  
10 differential equations, and I had really good  
11 instructors, and I worked hard, and we worked  
12 together as a team, at least I could begin to  
13 understand this problem and work through it. But  
14 someone had to teach me how to do it. I just  
15 couldn't look at it and know how to solve it.  
16 It's the same with pain. We can't expect  
17 people to just go, "Oh. Learn to live with it,"  
18 and they're going to say, "Okay. I can do that."  
19 We need to teach them how to do that, and that's  
20 been the missing tool for so long, is don't tell  
21 me; teach me how to do it.  
22 One of the problems today, if you go back to

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

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

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

22 I know that the National Pain Strategy was

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

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

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

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

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

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

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

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

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

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

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

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1 need more than just tapering. They need to be  
2 taught how to manage their pain and other  
3 interventions that may be necessary. They may need  
4 surgery. There are a lot of things, both by the  
5 healthcare professionals and even through  
6 self-management. They need to know how to manage  
7 their pain.  
8 Really what we need is a balanced approach,  
9 and that's the thing that I think, since the very  
10 beginning when I started the American Chronic Pain  
11 Association, we have never changed, the way we look  
12 at pain management. It's always been that balanced  
13 approach, combining all of the different things.  
14 We teach a lot of different skills, and it's  
15 up to the individuals which one they need. It's  
16 not like you follow this line, or you follow this  
17 pattern, or this one. It depends on what  
18 individuals need because each of us are different.  
19 Our needs are different, our pain is different, our  
20 lifestyles are different. We each need different  
21 things, but we need to be able to offer all of them  
22 in that balanced approach.

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1 One of the ways that we help people  
2 understand what it means to have a balanced  
3 approach to pain management is by using an analogy  
4 of a car, except a person with pain is like a car,  
5 but their car has four flat tires. Our expectation  
6 is all we need is that one quick fix, that pill, or  
7 one treatment or therapy, and we're good to go.  
8 The problem is it only puts air in one of our  
9 tires. And it may do exactly what it's meant to  
10 do, and it's doing a great job, but the problem is  
11 we still have three flat tires. We cannot go  
12 anywhere.  
13 So the question is, what else do we need?  
14 As I said, everybody is going to be different. It  
15 could be physical therapy; it could be counseling;  
16 it could be nutritional guidance; it could be  
17 acupuncture; it could be stress management; it  
18 could be a peer-led support group.  
19 When people get all four tires filled, it's  
20 up to them to maintain their car. You don't take  
21 your car back to the dealer and say wash my  
22 windshield or fill her up. That's our job. If

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1 something goes wrong with the car, then we take it  
2 in for a checkup. You see, it's a combination of  
3 treatments and therapies with the person with pain  
4 at the center of that, part of the treatment team.  
5 It gets them up and gets them going.  
6 I'm sorry this slide didn't go out right.  
7 This is our website. It's the [acpa.org](http://acpa.org); that's  
8 [T-H-E-A-C-P-A.org](http://T-H-E-A-C-P-A.org). You're welcome to visit it. We  
9 have a lot of tools, and that video, the car thing  
10 I just told you, is actually an animated video. I  
11 want to thank you for your time and your attention.  
12 DR. CHAI: Thank you, Ms. Cowan. This is a  
13 sensational presentation. You've provided us so  
14 much insight and information. Thank you so much  
15 for really highlighting and reinforcing how  
16 important it is to get the science right, and  
17 really why we are here today and tomorrow.  
18 Thank you, Ms. Cowan.  
19 MS. COWAN: Thank you.  
20 DR. CHAI: Yes, thank you.  
21 DR. CHAI: We will now hear from Corinne  
22 Woods for an Overview of Current Applications and

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1 Uses of MMEs. What you will see is as we go  
2 through all our presentations over the next two  
3 days, the presentations will build on each other  
4 and really reinforce the science and our goals of  
5 what we're trying to achieve. Thank you.  
6 Presentation – Corinne Woods  
7 MS. WOODS: Hi. Good morning. My name is  
8 Corinne Woods, and I am one of the team leads on  
9 the Drug Utilization Team in the Office of  
10 Surveillance and Epidemiology at CDER in FDA.  
11 Today I will present an overview of current  
12 applications and uses of morphine milligram  
13 equivalents in the U.S. Some topics I will touch  
14 upon are the use of MMEs in clinical practice, as  
15 well as some state regulations which may influence  
16 opioid prescribing. I will also provide an  
17 overview of how MMEs are used in dispensing and  
18 reimbursement, as well as in research.  
19 MMEs may be used in clinical practice, and  
20 we will hear more about this later in other  
21 presentations. Practitioners, when treating  
22 patients with opioid products, may use opioid



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

9 Another area where MMEs are used are state  
10 regulations. Forty-three states have limits on the  
11 amount or duration of opioids prescribed or  
12 dispensed. Of these, 15 states have MME-based  
13 limits as well. Some examples are a lowest  
14 effective dose; a limit of 30 MMEs per day for a  
15 patient's first opioid prescription; a limit of  
16 100 MMEs per day for all opioid prescriptions; and  
17 a limit of a certain total MME in a prescription,  
18 depending upon the severity of the patient's pain.

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

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

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

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

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

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

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

22 MMEs are used in some areas of research

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

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

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

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

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1 the second prescription an early refill in addition  
2 to the current therapy? Is a gap between two  
3 prescriptions caused by as-needed use or an  
4 interruption in therapy?  
5 The metric MMEs per day is often calculated  
6 using a day's supply value, which is typically  
7 entered by pharmacy staff and can be influenced by  
8 the prescriber's instructions or insurance  
9 requirements. Oftentimes, pharmacy staff will  
10 select a day's supply based on maximum dose  
11 allowable.  
12 In conclusion, MMEs are widely used in many  
13 areas of health care and research in the U.S. MMEs  
14 play a role in various prescribing limits across  
15 several states. MMEs can affect prescription  
16 dispensing and reimbursement and may directly  
17 influence patient care. Lastly, researchers may  
18 wish to consider real-world use patterns when  
19 calculating metrics involving MMEs for their  
20 analyses. Thank you for your attention.  
21 DR. CHAI: Thank you, Corinne, for the broad  
22 overview of the many applications and uses of MMEs.

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1 You made it very clear that we will need to keep  
2 all these different applications in mind as we  
3 discuss the science.  
4 We will now hear from Dr. McPherson, who  
5 literally wrote the book on opioid conversion.  
6 Welcome, Dr. McPherson.  
7 DR. McPHERSON: Good morning again. I'm  
8 delighted to be with you. Thank you for inviting  
9 me.  
10 DR. CHAI: I think you have a bit of an  
11 echo.  
12 AV TECH: No, she doesn't. That was another  
13 participant who was unmuted.  
14 DR. CHAI: Oh, okay. Thank you.  
15 Sorry about that. Go ahead, please.  
16 DR. McPHERSON: Okay. Take 3. Here we go  
17 again.  
18 Presentation – Mary Lynn McPherson  
19 DR. McPHERSON: Thank you so much for  
20 including me in this meeting. It's a pleasure to  
21 be here with you.  
22 As you know, my name is Lynn McPherson, and

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1 I'm a professor at the School of Pharmacy, and my  
2 practice is primarily in hospice and palliative  
3 care. I practiced my whole career in ambulatory  
4 care as well, and I'm very much interested in  
5 opioid conversion calculations.  
6 This is my objective, my goals for this  
7 morning and the time we have together, to give you  
8 a brief history of opioid conversion calculations  
9 and talk a little bit about the problems with doing  
10 these calculations, a new paradigm that I have  
11 recommended in a second edition of my book. Then  
12 at the very end, I'm going to share with you some  
13 late-breaking data from research in my hospice,  
14 looking at a 10-year history of the use of opioids  
15 in this population.  
16 Well, I think by now we all know what MME  
17 is, morphine milligram equivalent, and Dr. Woods  
18 just did a great job talking about all the  
19 scenarios where we would need to calculate an MME.  
20 In my world, it's primarily patient care, which  
21 we'll talk more on the subsequent slides. But I  
22 think several of the speakers who preceded me have

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1 talked about the guidelines and the state limits,  
2 which speak more to trying to limit the harm caused  
3 by the opioid crisis. We hear that over a hundred  
4 people a day die from an opioid overdose. I'm not  
5 so sure how much it's the miscalculation that's  
6 involved there. I think, certainly, that's a  
7 multifactorial issue by all means.  
8 Certainly, when we are looking at, for  
9 example, the CDC's intent guideline and state  
10 limits, the MME limits are intended to help  
11 clinicians make safe appropriate decisions  
12 regarding changes to opioid regimens, I think  
13 there's way more to it than, obviously, just an MME  
14 if that's what you're looking for.  
15 Certainly, the MME per-day metric can  
16 hopefully be used as a gauge of overdose potential,  
17 certainly indicating those patients where maybe the  
18 clinician needs to up their game a little bit in  
19 terms of closer monitoring, or reducing, or  
20 tapering opioids if it's clinically appropriate,  
21 and certainly prescribing naloxone if it's  
22 appropriate and any other risk mitigation

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

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

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

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

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

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

14 Mostly we talk about oral bioavailability.  
15 You can look at morphine. We say it's about 30 to  
16 40 percent. So if someone takes 10 milligrams of  
17 oral morphine, when you take a drug by mouth, it  
18 goes down and gets absorbed from the GI tract. The  
19 first place it goes is into the hepatic  
20 circulation.

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

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

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

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

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

22 Where did this come from? If you look at

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

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

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

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

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

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

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

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

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1 of these were kind of tertiary references. So  
2 basically, Von Korff was a tertiary reference of  
3 tertiary references, and then the CDC embraced  
4 those.  
5 So, you know, it kind of really boils down  
6 to the burning question.  
7 This really boils down to the burning  
8 question. Are opioid conversion calculations set  
9 in concrete? I know that my pharmacy students when  
10 we talk about drug math, they're so excited because  
11 they think, "Oh, my gosh. Drug math is one right  
12 answer." And in so many areas of drug math and  
13 pharmacy, that is true; there's one right answer.  
14 But, you know, I think when we talk about opioid  
15 conversion calculations, I think we're on a little  
16 bit shakier ground. I don't think it's quite that  
17 cut and dry.  
18 So as you heard from the kind introduction,  
19 I did write a book on opioid conversion  
20 calculations. This is the cover to the first  
21 edition, 2010. And as you'll see, the chart that I  
22 recommended at that time is very consistent with

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1 what the CDC is using. I went along with the flock  
2 because, frankly, at that time, in 2010, this was  
3 the best evidence, really, that we had. But I did  
4 spend the rest of the book talking about it's not  
5 just about setting up this ratio, and even that  
6 freaks out a lot of people. So if you're really  
7 freaked out about that, let's call a third grader,  
8 and they'll do that for us.  
9 That's not why we went to medical pharmacy  
10 nursing school or whatever professional school we  
11 went to. It is so that we could critically think  
12 through this process and consider all the variables  
13 typed here: the heterogeneity of opioid receptors;  
14 the quantitative difference in metabolic enzymes  
15 from person to person, anywhere from an 11 to a  
16 30-fold difference from person to person when you  
17 talk about the cytochrome p450 system; so complete  
18 and total variability of the pharmacokinetics and  
19 pharmacodynamics of opioids.  
20 Not to mention the difference in opioid  
21 responsiveness in different types of pain. I mean,  
22 opioids are not always the answer in neuropathic

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1 pain; it's only partially responsive. I think a  
2 big one for me is where the heck did this data come  
3 from? As a matter of fact, we're very excited to  
4 be launching a PhD in palliative care this fall.  
5 We're planning our first course, and part of that  
6 is looking at where did hospice and palliative care  
7 come from, what are the origins, where are we now,  
8 and what does the future look like?  
9 I had the opportunity to speak with  
10 Dr. Robert Twycross from the United Kingdom. I  
11 understand the UK is on the line here today. He is  
12 absolutely brilliant. He posed a question to me  
13 and, whew, thank goodness I knew the answer.  
14 He said, "Do you know the really early  
15 charts of equianalgesia said that 10 milligrams of  
16 parenteral morphine was equal to 60 milligrams of  
17 oral morphine. So why do all these charts today  
18 run around saying it's 10 and 30?" I said,  
19 "Because when people first thought that 10 to 60,  
20 it was based on a single-dose study."  
21 If we take any one of you today and give you  
22 some painful insult, and say 10 milligrams of

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1 parenteral morphine would be necessary to  
2 adequately treat that pain, and we all came back  
3 next week at this time and gave you the same  
4 painful insult, that would take 60 milligrams. But  
5 we've since learned that with chronic dosing, the  
6 sixth glucuronide metabolite actually is a super  
7 spinal analgesic, so really it's closer to this  
8 10 to 30.  
9 So single-dose studies, multiple-dose  
10 studies, it's drawing from pharmaceutical industry,  
11 and it's certainly my personal impression that when  
12 a pharmaceutical manufacturer publishes and they're  
13 prescribing information, an equianalgesic  
14 recommendation to convert to their product, they're  
15 being conservative because they don't want to harm  
16 anybody either. But it was never their intent that  
17 you use their equianalgesic guidance to go to their  
18 product to use it in reverse; so lots of different  
19 sources here.  
20 Nowhere does this chart consider  
21 patient-specific variables, so if the patient has  
22 comorbidities; do they have renal impairment;

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1 hepatic impairment; are they young; are they old;  
2 are they skinny; are they fluffy? What's the  
3 scoop? Other medical factors.  
4 The big question is, do we have  
5 bidirectionality? I just mentioned my concern  
6 about the CDC guidance. With methadone in  
7 particular, I do not think that it's taking into  
8 consideration bidirectionality.  
9 So I did the second edition that came out  
10 very late in 2018, and I made a few tweaks to the  
11 chart. As you can see here, morphine,  
12 10 milligrams parenteral, which includes IM, IV,  
13 and subQ because it's close enough for government  
14 work, although I think an IM opioid should be voted  
15 off the island. Instead of being 30 milligrams of  
16 oral, I bumped it down to 25, and we will talk  
17 about that.  
18 I have to tell you, there's been tremendous  
19 uptake of this new chart with the notable exception  
20 that people whine audibly that they can't divide or  
21 multiply in their head by 2 and a half. Again,  
22 call the third grader.

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1 The big, big change is looking at  
2 hydromorphone. Hydromorphone from parenteral to  
3 oral is really 1 to 2.5; it is not 1 to 5. And  
4 consequently, based on excellent data now,  
5 2 milligrams of parenteral hydromorphone is about  
6 25 of oral morphine, as it's not really a 20 to 1  
7 ratio. This has been kind of a wake-up call for a  
8 lot of people.  
9 So let's look at some of this data. What is  
10 the deal, first off, with the IV-to-oral morphine?  
11 We've had 10 to 30 for probably 30 years, so how  
12 dare I make it 1 to 2.25 or 10 to 25. Actually,  
13 the data does support that the equianalgesic table  
14 with this ratio is anywhere from 1 to 2 to 1 to 3.  
15 Kalso in 1990 showed that 20 or 30 of  
16 morphine by mouth was about 10 milligrams IV or  
17 subQ. Starlander in '11 said it works out to  
18 1.1 to 2, but that was only 11 patients so I can't  
19 get too misty over that. Takahashi in 2003 said,  
20 well, somewhere between 1 to 2 and 1 to 3, based on  
21 a lot of patient-specific variables. And I'm very  
22 fond of, as you'll see in a moment, the practice of

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1 what they do at MD Anderson Cancer Center, because  
2 they do this all the time. They see 10 milligrams  
3 of parenteral morphine is 25 of oral morphine.  
4 As you can see, this is an abstraction from  
5 the chart that I used. I am arguing that  
6 10 milligrams of parenteral is 25 of oral. That's  
7 not to say that 10 to 30 is incorrect. Frankly,  
8 sometimes I'll even do the one-third if I'm on the  
9 fly because I know I'm going to probably do a dose  
10 reduction, or perhaps it works out that way to get  
11 to the next reasonable dosage formulation or tablet  
12 strength.  
13 Alright. So what's with the  
14 morphine-oxycodone thing? We've always said for  
15 30 years, 30 of morphine is about 20 of oxy.  
16 What's the deal? So does 25 of morphine work out  
17 to be 20 of oxy? Can I do that? Am I going to go  
18 to jail? What's the scoop?  
19 We do know that there's tremendous  
20 variation, as I showed you several slides ago, in  
21 the bioavailability of these drugs. Morphine, in  
22 particular, is highly variable. Oxycodone is

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1 60 percent or more. On average, it's about  
2 80 percent. So really, you will find charts that  
3 say oral morphine or oral oxycodone are exactly the  
4 same potency. It goes anywhere from 1 to 1 to  
5 2 to 1. Really, it just depends on the patient's  
6 ability to absorb the opioid. So I'm very  
7 comfortable with 25 of morphine is about equivalent  
8 to 20 milligrams of oral oxycodone.  
9 Alright. What about this one? This is a  
10 big one, parenteral oral hydromorphone. Really,  
11 this is a whole question of bioavailability. And  
12 if you look at super old data, 1987-1988, it's  
13 about 50 percent. Now, I will grant you there was  
14 a very large degree of variability when you look at  
15 the bioavailability, so we have to keep that in  
16 mind. But it's really not that 5 to 1; it's closer  
17 to 1 to 2 and a half, as shown in my chart here.  
18 So do we need to evaluate the conversion  
19 from oral to parenteral? No, I would argue  
20 because, really, it's determined by the  
21 bioavailability, and secondarily by  
22 pharmacogenetics. Clinical guidance in large

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1 patient populations has provided average guidance  
2 with the best being 1 to 2.5 with IV to oral.  
3 This is probably the biggest game changer  
4 that drove the changes I made in the recommended  
5 chart. This is data from my very dear friend,  
6 Akhila Reddy, who's a physician at MD Anderson, and  
7 she really did a very fine job with this research  
8 looking at many, many patients at MD Anderson,  
9 retrospectively; patients who had been on  
10 IV hydromorphone, and what would be the equivalent  
11 if we switched to either oral hydromorphone or on  
12 morphine or oral oxycodone. She did see some  
13 biomodal distributions here, 1 milligram of IV  
14 hydromorphone. If the patient was on less than  
15 30 milligrams a day of IV hydromorphone, it turned  
16 out to be 2.5 of oral.  
17 So that is exactly what I've reflected in  
18 the chart. If it's greater than 30s, it's a smidge  
19 or less, which I keep in the back of my mind. If  
20 you're going to oral morphine, it came out to a  
21 little more than 11 and a half or so, unless  
22 they're on a very high dose, and then she also did

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1 it for oxycodone.  
2 So her bottom line, if you look at the  
3 bottom left of this slide, 1 to 2.5 IV-to-oral  
4 hydromorphone. They used the 1 to 10, which  
5 they've used historically for years at MD Anderson.  
6 I made it 1 to 12 and a half to make the chart  
7 work, and then 1 to 8 for IV hydromorphone to oral  
8 oxycodone.  
9 I don't know. If I write a third edition to  
10 this book, will I even have an equianalgesic chart?  
11 Should it be a ginormous chart where you go over a  
12 row and down a column, and it's a very specific  
13 ratio for that particular opioid you're coming from  
14 and to, and dependent on the route of  
15 administration? I don't know. But I tend to think  
16 that might confuse people even more.  
17 So I really did struggle very hard to keep  
18 the equianalgesic chart to make it the safest and  
19 the easiest for practitioners, and of course  
20 patients is the bottom line.  
21 So here's the elephant in the room. What  
22 about the morphine hydromorphone? What about the

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1 bidirectionality issue here? Is it bidirectional?  
2 If you go from IV hydromorphone to oral morphine,  
3 is it the same if you're going in reverse?  
4 One study by Lawlor looked at subQ to subQ  
5 hydromorphone and morphine, and back again, and  
6 oral to oral. So when you're going from morphine  
7 to hydromorphone using the same route, regardless  
8 of which it was, it turned out to be about 5 to 1.  
9 When you're going from hydromorphone to morphine,  
10 it was closer to 4 to 1.  
11 But even Lawlor in that study said, "Look,  
12 this data is highly skewed and variable. It's not  
13 at all normally distributed." So they argued that  
14 this data was not clinically significant, the small  
15 difference we saw in bidirectionality.  
16 Then I'll get this question once in a while.  
17 Okay. If you're switching somebody from  
18 10 milligrams a day of IV hydromorphone to oral  
19 morphine, and you use the old chart -- which, I got  
20 to tell you, most people still use -- it calculates  
21 out to 200 milligrams of oral morphine.  
22 So if your mama is getting 10 milligrams of

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1 IV hydromorphone and it's time to go home, are we  
2 really going to put mom on 200 milligrams of oral  
3 morphine? Or if you look at the next column over,  
4 you could use what I'm proposing, which would be  
5 the 2 milligrams of parenteral hydromorphone, which  
6 would be 25 or oral morphine, it works out to  
7 125 milligrams of oral morphine.  
8 So you would say, well, the new conversion  
9 is more conservative, and I would argue is very  
10 much more consistent with Dr. Reddy's data.  
11 Now, what about switching back? If someone  
12 is on 200 milligrams of oral morphine and you need  
13 to switch them to IV hydromorphone, the older  
14 method would say that's only 10 milligrams, of  
15 course, because we're doing it in reverse, but the  
16 newer method would say 16. So the new conversion  
17 seems more aggressive, obviously, than the older  
18 conversion ratio.  
19 But I would argue there is more than one way  
20 to pluck a chicken. If you take 200 milligrams of  
21 oral morphine, we have pretty good data that going  
22 from oral morphine to oral hydromorphone is a 5 to

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1 1 ratio. So if you take 200 milligrams of oral  
2 morphine, that's going to be 40 milligrams of oral  
3 hydromorphone, which if you look at the  
4 bioavailability data of hydromorphone is  
5 16 milligrams of IV hydromorphone. Boom! So  
6 that's how I came up with these numbers.  
7 What do I think about this chart? I think  
8 the chart that I have proposed here is about the  
9 best you can do with what we currently know. But I  
10 always say -- when you say what's the magic  
11 dose -- it's sort of like saying which one is my  
12 seat?  
13 I don't know. My job was to get you in the  
14 ball park. Your job is to put on your big-girl  
15 pants here and use that big old brain of yours, and  
16 all that critical thinking that you learned about  
17 in medical pharmacy, nursing school, wherever you  
18 went to school, and look at your patient and think  
19 through what do I do with this number. I mean, you  
20 calculate a number. You can either go with that  
21 number. You can increase it or you can decrease  
22 it. So I think you have to use some critical

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1 thinking skills.  
2 So here's the big question. Have  
3 practitioners gotten their arms around this  
4 practice? Well, let's take a look. This is one of  
5 my current residents, Dr. Cindy Ngyuen. This was  
6 one of her two projects this year, and I think she  
7 did an awesome job. This was an online survey. I  
8 love the title even. It's called, Not So  
9 Surprising: The Inconstancy -- I love that new  
10 word -- of Oral Morphine Equivalent Calculations.  
11 So again, this was an online survey to  
12 self-reported healthcare clinicians who dispense,  
13 administer, or prescribe opioids. The aim was to  
14 explore the practices, perceptions, and potential  
15 barriers to perform safe and effective opioid  
16 conversion calculations to calculate a patient's  
17 total daily oral morphine equivalent. We called it  
18 OME.  
19 We had 406 people respond. We were really  
20 tickled. As you can see, 28 percent were advanced  
21 practice providers; 17 percent were RNs;  
22 34 percent, pharmacists; and 22 percent were

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1 physicians. The respondents reported 99 percent of  
2 them said, "To be able to accurately calculate an  
3 OME is highly important," and 94 percent said they  
4 were strongly confident in their OME calculation.  
5 The study was actually much larger than what  
6 I'm reporting here, but I'm just giving you the  
7 highlights. We asked them about which of the  
8 following is a barrier, in your opinion, to  
9 performing a safe and effective and a highly  
10 accurate, highly important calculation?  
11 As you can see here, 51 percent said,  
12 "Finding the best equianalgesic data is a problem"  
13 in a little over half of the respondents; clarity  
14 on when to dose-reduce the calculated dose, again,  
15 a little bit more than half struggled with that;  
16 confidence in the accuracy of an online calculator,  
17 again, a little more than half. Personally, I  
18 think that should be a 101 percent.  
19 What about particular opioids? What do you  
20 do with transdermal fentanyl? What do you do with  
21 transdermal fentanyl if the patient weighs  
22 80 pounds? How about my girl methadone? How about

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1 somebody on a ridiculously high dose of an opioid?  
2 I know working in hospice, we often get  
3 patients referred to us because the other  
4 healthcare team, they don't know what to do  
5 anymore. We get somebody on 30 milligrams an hour  
6 of IV dilaudid and it's not working, we don't know  
7 how to fix it, so they turf the patient to hospice.  
8 The last is uncertainty of the patient's  
9 medication adherence. I've certainly been burned  
10 by that, where we had one patient, an older woman,  
11 and her son was taking care of her. He reported to  
12 the nurse what he was giving his mother, which was  
13 a PRN morphine dose.  
14 The nurse asked me to do a calculation to  
15 methadone. I did it, and the older woman became  
16 very, very sedated and was on the road to flat-out  
17 toxicity, only to find out the son had made all of  
18 that up because he didn't want the nurse to think  
19 he was a bad son. So, great. I almost killed the  
20 patient because he didn't want to look bad.  
21 Then we asked them how often do you do a  
22 calculation. Forty percent said daily. Another,



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

9 So how would you calculate the total daily  
10 dose of morphine here? Would you, A, say it's  
11 150 a day based on using the extended release as  
12 scheduled and all of the allowable immediate-  
13 release morphine PRN doses; or would you say I'm  
14 just going to count the schedule because I don't  
15 know how much of the MSIR they're going to use; or  
16 would you eyeball the patient and say, "Well, in my  
17 professional opinion, I think they're obviously  
18 going to use the extended release, which is  
19 scheduled, but this is how much of the immediate  
20 release I kind of think they're going to use."

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

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

10 Alright. This was a study -- Dr. Jeff Fudin  
11 is speaking today. His resident and my resident  
12 did this survey where we also did a survey on  
13 social media advertising to professional  
14 organizations. 319 participants took the study,  
15 and we asked them simply, look at these  
16 8 prescriptions right here, these 8 opioids with a  
17 different range. Could you tell us -- just type it  
18 into the box -- the estimated morphine equivalents?  
19 So we did hydrocodone, 80; transdermal  
20 fentanyl, 75; methadone, 40; oxycodone, 120; and  
21 hydromorphone, 48. And as you can see here, there's  
22 quite a bit of variability.

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

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

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

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

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

5 We did have various scenarios, which I'll  
6 show you in a moment. And talk about a nice  
7 capture of data here, 370 responses from  
8 53 countries. I'm not going to read this to you,  
9 but I'll just let you kind of take this in.

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

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

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

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1 interesting, though, looking at the international  
2 flavor here. It's not consistent across the board.  
3 Morphine's pretty tight. IV-to-oral morphine, in  
4 the U.S., the median and the mode is 3; in Canada  
5 it's 2 and 2; in the UK it's 2 and 2. So I feel  
6 like a big winner because I went with that 2.3.  
7 As you can see, there's a big difference in  
8 the U.S. We say IV-to-oral hydromorphone is a 1 to  
9 5 ratio when in fact Canada and the United Kingdom,  
10 where we had the next most highest responses, they  
11 were very tight, 2 and 2, which again in my chart I  
12 have 1 to 2.5. So me and Canada and the UK, we are  
13 tight. We got it going on. So as you can see,  
14 there's a lot of variability cooking with this.  
15 Alright. So I know you're sitting there  
16 thinking, "Why are you banging your head on the  
17 table?" There's an app for that. Of course,  
18 there's an app for that. There's an app for  
19 everything.  
20 I remember years ago I had a pharmacy  
21 student on rotation with me, and we just wrapped up  
22 team meeting, and one of the nurses said, "Hey.

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1 Could you do this calculation for me?" And I said,  
2 "Oh, this is great for the students." So I turned  
3 to the young man, and I said, "Could you do this  
4 calculation for the nurse?" And he said, "Oh sure.  
5 I've got an app for that," and I said, "Of course  
6 you do."  
7 So he goes through the math, and I hear him  
8 inhale sharply, and I said, "What's the scoop?"  
9 And he said, "Wow! This is unbelievable." I said,  
10 "What did you come up with?" He said, "It's like  
11 almost a million milligrams of morphine." I said,  
12 "Well, what do you think of that number?" He said,  
13 "Well, I think we're going to have to order more  
14 morphine."  
15 I cannot make this stuff up. So clearly  
16 somebody disengaged their brain, so what do we  
17 think about online conversion calculators?  
18 This is a very nice study looking at a  
19 variety of calculators, and as you can see in the  
20 blue box, across the top we see six or seven  
21 different online conversion calculators, and going  
22 down in the columns, we have different features.

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1 So all but one do the opioid calculation for  
2 you. Not all of them share the data that informs  
3 their algorithm by giving the equianalgesic table.  
4 Not all of them will let you convert from multiple  
5 opioids as we frequently do. Only two of them  
6 account for acute and chronic dosing with morphine  
7 and methadone, and transdermal fentanyl,  
8 buprenorphine, methadone, tapentadol, not included  
9 routinely in all of them.  
10 Here's a big one for me, the ability to  
11 dose-reduce because of incomplete cross-tolerance.  
12 That's critical in my opinion. Then a couple of  
13 them, most of them, half of those I guess are  
14 available for a smartphone.  
15 So this study is also looking to compare and  
16 contrast these calculators; identify the  
17 mathematical disparities; and compare automated  
18 conversions against manual calculations revealing  
19 potential risks and making recommendations. As you  
20 can see, the variation range is from minus  
21 55 percent to 242 percent. Wow! That's amazing.  
22 As I said just a moment ago, at my

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1 university we offer an online master of science  
2 degree in palliative care, and actually as we  
3 speak, we are in week 2 of PALC 615, which is the  
4 advanced pain management course, and we just last  
5 week did this exercise.  
6 But this is data looking at variability  
7 among online opioid conversion calculators  
8 performing common palliative care conversions.  
9 This study -- which we're just now responding to  
10 reviewer comments, and I'm pretty sure it's going  
11 to be published, accepted for publication, when  
12 we're done that -- we looked at the cohort of  
13 students. It was about 50 students each summer in  
14 2018 and '19 and how they handle this.  
15 The way the discussion question went was,  
16 first, what do you think of online opioid  
17 conversion calculators? Second, here are three  
18 hypothetical problems -- and again, I just want to  
19 point out the problem, that these are not about the  
20 therapeutics, like, "Oh, I would have added a  
21 steroid instead," it's all about the math -- and  
22 take these three problems; find any three opioid

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1 conversion calculators online; run these three  
2 scenarios; and record your results.  
3 The next question is, what do you think  
4 about how these calculators did from calculator to  
5 calculator? And the last question is, now what do  
6 you think about online conversion calculators?  
7 Here's the data. As you can see the three  
8 cases, the first case is a 78-year-old woman  
9 getting transdermal fentanyl 75 mcgs. The patient  
10 doesn't seem to be responding despite dose  
11 increases. She is 5 foot 4 and weighs 82 pounds.  
12 And again, this is a program for people getting a  
13 master's degree in palliative care. We have people  
14 getting palliative care and on hospice who are  
15 5 foot 4 and weigh 82 pounds, so if you don't ask  
16 about the body habitus, you are not doing your job.  
17 The ask was to convert to long-acting oral  
18 morphine and determine a dose of short-acting for  
19 breakthrough pain. So in each of these scenarios  
20 you will see the first one is the record value,  
21 which is what we calculated, and you'll see three  
22 numbers. For example, you see 40, 60, and 80

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1 there.  
2 So again, 75 mcgs would be about 150 to  
3 180 milligrams of oral morphine equivalents, but  
4 because this patient is cachectic and we know that  
5 you nowhere get the bang for the buck you would  
6 expect, we empirically reduce it. So the best  
7 answer would probably be around 60 milligrams of  
8 oral morphine.  
9 But then we did our own little interquartile  
10 range kind of deal empirically here and said,  
11 "Well, anywhere between 40 and 80 we would consider  
12 as being in the range." But then if you look at  
13 the most popular conversion calculators like  
14 Practical Pain Management; GlobalRPh; ClinCalc; the  
15 Oregon one; Agency Medical Director's Group, look  
16 at the range. Holy moly! There is huge disparity  
17 there.  
18 The second one was a 58-year-old man with  
19 end-stage lung cancer getting IV hydromorphone at  
20 6 milligrams an hour, and we see this all the time.  
21 He's using his 3-milligram bolus about 3 times an  
22 hour, so this guy is getting 15 milligrams an hour,

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1 on average, of IV hydromorphone. And the pharmacy  
2 just called and said, "Well, you used the last drop  
3 of IV hydromorphone in the entire state; you're  
4 going to have to switch."  
5 So the patient can swallow, so let's switch  
6 him to oral morphine. So it calculates out to  
7 about 3600 milligrams of oral morphine, but as you  
8 can see, our reference value in the middle is 2250  
9 because we did reduce for cross-tolerance; so in  
10 the center there, that's about a third reduction,  
11 but then we have our two endpoints as well. But  
12 you can see in the next calculator, it's all the  
13 way up to 6,000 milligrams. That's the range we  
14 saw from the students.  
15 The last one is a patient on MS Contin and  
16 MSIR. The pain seems to have a neuropathic  
17 component, so we want to convert to oral methadone,  
18 so we use very straightforward conversion. But as  
19 you can see, look at the Oregon one; quite a bit of  
20 variability with that.  
21 The last thing I want to share with you from  
22 this study is, looking at dosing and reduce

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1 tolerance for all these scenarios, if you'll look  
2 at the dosing of the immediate release, 5 percent  
3 wanted to give the immediate-release opioid longer  
4 than every 4 hours, and half of them said every  
5 4 hours.  
6 Looking at cross-tolerance in scenario  
7 number 1, which is the transdermal fentanyl,  
8 60 percent wanted to reduce for cross-tolerance  
9 when in fact the data and form is really that's not  
10 necessary, and the same with scenario C. So it's  
11 kind of all over the place with this as well.  
12 This is the five-step process that I argue  
13 is a good way to go when doing an opioid conversion  
14 calculation. It was part of Arnold Gammatoni's  
15 study here years ago. We published this in 2003.  
16 When someone calls me, I really do these  
17 five steps. When a nurse or a doctor calls me,  
18 I'll say, "Tell me about the pain," because  
19 sometimes the answer is, "You don't even need to do  
20 a conversion calculation. The patient has  
21 screaming metastatic bone pain. Have you thought  
22 about adding a nonsteroidal or a steroid to help

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1 with that pain?"

2 So assess the patient's pain. Is even an

3 opioid the correct drug to be using? Let's start

4 at the 20,000-foot view. Then I want to know

5 certainly about the severity, because when I get

6 down to step 4, I need to know was the patient in

7 pain, was their pain controlled, and maybe we're

8 switching because of the side effects. You need to

9 know about the patient's pain.

10 So you're determining if the situation is

11 uncontrolled pain, worsening of the pain, is it a

12 new kind of pain, and maybe you need an adjuvant

13 drug because it's neuropathic.

14 The next is to determine the total daily use

15 of the current opioid. This should include all

16 scheduled, all long acting, as well as an average

17 utilization of breakthrough.

18 All the time, nurses will call me and say,

19 "This guy's on MS Contin 60 q12 and 20q2 PRN." I

20 say, "Okay. How much are they using in the PRN?"

21 I just told you, "20q2." I said, "No, you told me

22 the order. You did not tell me what the patient is

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1 getting on average."

2 Once in a while, it will be, "Well, I don't

3 know. They're being discharged from the hospital.

4 They came right here from the hospital. How can I

5 tell?" I said, "You pick up the phone and you call

6 the nurse in the hospital where he came from, and

7 if you can't get that data, the PRN, I don't

8 include it in the calculation."

9 Now the reason 3 is in black is because I do

10 believe an online calculator can do number 3 for

11 you. After you decide what you want to switch to,

12 this is a simple ratio. This is the third-grader

13 step here. I do believe the online calculator can

14 do a nice job saying if 20 of this is 25 of that,

15 then 40 of this has got to be X, Y, Z, so I'm

16 trusting the computer to do that.

17 But then I really don't trust the computer

18 to do step 4 or 5, similar to step 1 and 2. The

19 computer spits up this number. So again, as I said

20 a few minutes ago, you can either run with that

21 number, rarely will we increase that number, or

22 often I decrease that number. So it depends on the

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1 situation.

2 If the patient's pain was very well

3 controlled on the current regimen and I'm just

4 switching formulations, and it's not a new

5 molecule, I'll probably just round down to the next

6 most convenient dosage formulation; what tablet

7 strength is it, is it available in, for example.

8 If I'm switching drugs, entirely switching

9 opioids, if they were not in pain and I'm switching

10 because of a side effect, I might cut back

11 50 percent because of lack of complete

12 cross-tolerance. If they were in pain, I'm not

13 going to cut back quite that much. Maybe I'll do a

14 quarter; maybe not even that much. It just

15 depends.

16 Step number 5 is to monitor your patient

17 like nobody's business, and you know no online

18 calculator is going to do that. They just walk

19 away. They're done. They're out of here. So you

20 follow the patient very carefully. As a matter of

21 fact, with methadone, we have a policy in the

22 hospice I work with that the nurse must visit every

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1 day for the next 5 days and go through the laundry

2 list of monitoring parameters to make sure the

3 patient is not developing toxicity.

4 If you don't see methadone toxicity it's

5 because you're not looking, because methadone does

6 give you fair warning. I know everybody snores,

7 but when the patient starts sucking the curtains

8 off the walls, this is a sign that all is not well.

9 So those are the five steps that I think are

10 very important and, again, an online calculator

11 will only do step number 3 for you. And since I'm

12 a hospice girl, I just wanted to share with you,

13 for fun, some of the data.

14 I have a huge database of data from a very

15 large hospice in the United States. We have a

16 database of every drug prescribed for a hospice

17 patient admitted to the hospice and the discharge

18 by death, which is about 85-90 percent of those

19 patients, over a 10-year period, 2010 to 2019.

20 We specifically looked at patients who were

21 prescribed an opioid, which is 137,000 patients.

22 The length of stay, our mean length of stay, is

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1 51 days; the median is 10 days. This is a problem  
2 with hospice today, is patients being referred and  
3 the hospice nurse hopes that they can get through  
4 the 4-hour admission visit before the patient dies.  
5 So I really wish we would all row in the same  
6 direction so that we could get patients in the  
7 hospice earlier, and they could really enjoy the  
8 hospice benefit.  
9       Anyway, I have got a ton of data, but I just  
10 wanted to share this with you, looking at the blue,  
11 which is at the time of admission, and the red is  
12 at the time of death. Again, our median length of  
13 stay is 10 days, but our mean is 51 days.  
14       I just arbitrarily came up with these  
15 MME buckets of less than 50 milligrams, 50 to less  
16 than 90, 90 to 199, and then I added 200 to 400 and  
17 over 400. So on admission, less than 50 was half  
18 the patients, 50 to 90 was 17 percent, and so  
19 forth.  
20       If you look at the time of death, 50 percent  
21 are still under the 90, but 90 to 199, and probably  
22 most of them are toward the lower end, that's

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1 25 percent of patients. And we still have a nice  
2 little chunk of people on higher than  
3 200 milligrams or even 400 milligram, or a morphine  
4 equivalent. I'm here to tell you, if you don't do  
5 hospice for a living, I promise you, some people  
6 die very, very hard. It can be very difficult.  
7       So in closing, what's the plan, Stan? I  
8 think we all have to be Boy Scouts here; okay,  
9 maybe a Girl Scout if you want to be fair balanced.  
10 I think there is so much more to opioid conversion  
11 calculations than the simple calculation itself.  
12 And don't get me wrong; I do love drug math,  
13 obviously, but I think we have to do a very careful  
14 assessment.  
15       Number one, is an opioid even really the  
16 best treatment for this patient, and to use the  
17 very best equivalency data that we can, that is  
18 based on science. I think mine is pretty awesome,  
19 but then, again, I would say that. But just use  
20 something that is fair balanced. I would not use a  
21 pharmaceutical industry's guidance in reverse from  
22 what they intended. I would never do that.

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1       The rule I roll with all the time is I'm  
2 very conservative with the schedule dose, but  
3 because I'm dealing with hospice patients, I tend  
4 to be crazy generous with the breakthrough dose.  
5 If it's an ambulatory patient with chronic  
6 non-cancer pain, the provider may choose to not  
7 even provide a PRN. It just depends on the  
8 clinical situation, or they may say you can take a  
9 Percocet every 4 hours as needed but not to exceed  
10 2 tablets a day. That just depends on the clinical  
11 scenario.  
12       I think we should be treating patients, not  
13 numbers. I think we should be vigorously  
14 monitoring the patient response, and I think we  
15 have to be very, very careful in those states that  
16 do have some arbitrary MME limits to consider how  
17 this will impact patient care. Thank you so much  
18 for your attention. I appreciate it.  
19       DR. CHAI: Thank you, Dr. McPherson. That  
20 was, frankly, amazing. You're a phenomenal  
21 speaker, and that was a tremendous amount of  
22 information that you've jammed packed into that

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1 time.  
2       We're actually a little bit ahead of  
3 schedule, so we're going to go ahead and take a  
4 10-minute break. When we return, we'll be hearing  
5 from Dr. Fudin.  
6       Dr. Fudin, will you be ok to start  
7 10 minutes early, at 11?  
8       DR. FUDIN: Yes, I will. Can you hear me  
9 ok?  
10       DR. CHAI: Yes.  
11       DR. FUDIN: Okay. Yes.  
12       DR. CHAI: So we're going to adjust a little  
13 bit in order to provide more time for either  
14 presentations or clarifying questions. Please plan  
15 to be back at 11 a.m. Thank you, everybody, and  
16 please remember to mute your phones.  
17       (Whereupon, at 10:51 a.m., a recess was  
18 taken.)  
19       DR. CHAI: Welcome back, everybody. I'd  
20 like to welcome Dr. Fudin, who has many years of  
21 experience in pain management and has published  
22 many articles in this space.

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1 Of note, Dr. Fudin will not be able to join  
2 us tomorrow for day 2. Panel members, please jot  
3 down any clarifying questions that you may have for  
4 Dr. Fudin today, as well as for our other speakers,  
5 to ask during the first clarifying question session  
6 today at approximately 12:10 p.m. Thank you.  
7 Dr. Fudin, go ahead, please.  
8 DR. FUDIN: Thank you, Grace. Can you hear  
9 me ok?  
10 DR. CHAI: Yes, I can. Thank you.  
11 DR. FUDIN: Fantastic.  
12 Presentation – Jeffrey Fudin  
13 DR. FUDIN: The topic I'm covering today  
14 will be Individual Patient and Medication Factors  
15 that Invalidate Morphine Milligram Equivalents.  
16 This next slide is a disclosure slide to show you  
17 various companies that I've worked for as a  
18 consultant. I do have to add Chempharm, which is  
19 just recent, and Collegium, which is just recent,  
20 after these slides were submitted.  
21 The objectives, at the completion today,  
22 hopefully you'll be able to explain opioid

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1 conversion calculations and strategies when  
2 developing a care plan for patients in chronic  
3 pain; assess patient-specific factors that warrant  
4 adjustment to an opioid regimen; identify important  
5 drug interactions that can affect opioid serum  
6 levels; and describe how pharmacogenetic  
7 differences amongst patients can affect opioid  
8 efficacy, toxicity, and tolerability.  
9 This next slide is really especially  
10 important. This slide delineates the various  
11 opioids by chemical class, and there are a few  
12 things I would like to point out here.  
13 First, is that if you Look in the first column of  
14 phenanthrenes, most of the commonly prescribed  
15 opioids are in that class; for example, morphine,  
16 hydromorphone, oxycodone, oxymorphone,  
17 buprenorphine, and even dextromethorphan and  
18 naloxone.  
19 There are a number of different drugs that  
20 are in that pharmacological class, and it's really  
21 important to recognize, for example, that there are  
22 very different drugs that are in that class.

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1 Unfortunately, there are a number of people that I  
2 consider anti-opioid zealots that will tell you  
3 that, for example, OxyContin is synthetic heroin.  
4 I've seen it in the press. I've heard it on auto  
5 podcasts and things like that. It's simply not  
6 true. Dextromethorphan is in that class, and so is  
7 naloxone, which blocks opioids.  
8 The chemistry is important. Dr. McPherson  
9 talked about the lack of therapeutic response or  
10 adverse effects. If you look over in the very last  
11 column --  
12 DR. CHAI: Dr. Fudin?  
13 DR. FUDIN: Yes?  
14 DR. CHAI: I'm sorry to interrupt you. I  
15 think we're a little bit off on your slides. I'm  
16 sorry to interrupt. We can try to orient you back.  
17 DR. FUDIN: Okay.  
18 DR. CHAI: My apologies.  
19 DR. FUDIN: Okay.  
20 DR. CHAI: Chidi, are you able to get us  
21 back on track with the slides?  
22 (Pause.)

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1 DR. CHAI: Well, it's a good thing we are  
2 ahead of schedule. We're just going to take a  
3 minute to try to get the slides back, because I  
4 think it's very important to be able to see the  
5 slides as you're walking us through.  
6 DR. FUDIN: Yes, okay.  
7 DR. CHAI: So please give us a minute.  
8 DR. FUDIN: Sure.  
9 DR. CHAI: Yes. Sorry about that.  
10 DR. FUDIN: That's okay.  
11 (Pause.)  
12 DR. CHAI: It's been a very interesting year  
13 this year, but we're fortunate to be able to have  
14 this meeting, despite having it virtually.  
15 (Pause.)  
16 DR. FUDIN: Great. Okay. It's looks like  
17 we're set, right?  
18 DR. CHAI: Yes. Thank you. Please go  
19 ahead.  
20 DR. FUDIN: We're on the slide of the  
21 chemistry. As I was saying, the first column is  
22 the majority of most commonly prescribed opioids.

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1 In that column, we see things like buprenorphine,  
2 naloxone, which obviously is an opioid blocker, and  
3 naltrexone, the same thing; and also  
4 dextromethorphan, over-the-counter cough syrup.  
5 But we also see things like morphine, oxycodone,  
6 and oxymorphone.  
7 Now, I started to mention that Dr. McPherson  
8 was talking about lack of therapeutic response. If  
9 you hop over to the third column, you'll see, for  
10 example, methadone. Now, methadone, which is a  
11 diphenylheptane, is a drug that not only has opioid  
12 activity but also blocks NMDA and blocks reuptake  
13 of norepinephrine and serotonin, which makes it  
14 particularly useful for neuropathic pain, probably  
15 more so than other opioids.  
16 What if you put a patient on methadone,  
17 though, they tolerated oxycodone before, but it  
18 didn't work? So you switch them to methadone, and  
19 the methadone worked, but they were sick to their  
20 stomach and had hallucinations.  
21 Well, it would be good then to put them back  
22 on a phenanthrene type opioid, in the first column,

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1 that had similar properties to methadone in terms  
2 of blocking NMDA, having opioid activity, and  
3 blocking reuptake of norepinephrine. And there is  
4 such a drug, and it's called levorphanol. So it's  
5 not just about switching one drug to another; it's  
6 also about the therapeutics.  
7 The other thing I want to point out is the  
8 third column over where we have the  
9 phenylpiperidines. There you have fentanyl, for  
10 example, and all the fentanyl derivatives. But you  
11 also have illicit fentanyl. Unfortunately, I've  
12 seen practices that have stopped prescribing  
13 fentanyl because they think that all the reports of  
14 fentanyl deaths are the same thing as  
15 pharmaceutical fentanyl. They are not. The  
16 fentanyl found on the street is very different,  
17 sometimes more potent than fentanyl and sometimes  
18 less potent.  
19 What are some of the general issues that we  
20 see with morphine equivalent daily doses, MEq's, or  
21 whatever you want to call it, and opioid  
22 conversions? Well first, there's a pharmacogenetic

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1 variability among patients. Not every patient is  
2 the same. We have to worry about drug  
3 interactions. We have to worry about lack of  
4 universal morphine equivalents, which Dr. McPherson  
5 nicely delineated for you, and also specific  
6 opioids that should never have a morphine  
7 equivalent daily dose.  
8 Those include:  
9 Methadone, because it has multiple  
10 mechanisms of action. Again, it's an opioid, a  
11 full-agonist opioid. It blocks reuptake of  
12 norepinephrine and it blocks reuptake of serotonin,  
13 which has no effect on pain, and it also blocks  
14 NMDA receptors, which are found in nerves.  
15 Buprenorphine. Buprenorphine is a partial  
16 agonist and also an antagonist to kappa receptors,  
17 but it has a very high affinity for the opioid  
18 receptor, higher than morphine. And I'm going to  
19 come to that on a couple of slides from now.  
20 Then tapentadol. Tapentadol is a  
21 full-agonist opioid, but it blocks reuptake of  
22 norepinephrine. It has about 18 times less than

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1 binding affinity to the morphine receptor compared  
2 to morphine.  
3 Then there's tramadol. Now, some people  
4 think that tapentadol is a glorified tramadol, and  
5 that couldn't be further from the truth. Tramadol  
6 has no activity until it's converted from its  
7 parent compound tramadol to o-desmethyltramadol by  
8 the cytochrome 2D6 enzyme in the liver. It has  
9 5 metabolites and heavily relies on the CYP system  
10 in the liver to metabolize it, whereas tapentadol  
11 does not require phase 1 metabolism at all, so  
12 there's less drug interactions.  
13 I mentioned to you that tapentadol was  
14 18 times less the binding affinity to the  
15 mu receptor compared to morphine. Tramadol is  
16 6,000 times less. So yes, they have the same  
17 chemical nucleus but, no, they are not the same  
18 drug. They are very, very, very different. And  
19 anybody who thinks that tramadol could be a  
20 substitute for a full-agonist opioid needs to do  
21 some studying.  
22 This next slide, conceptual dose-response

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1 curves of three different opioids, what I did in  
2 this slide -- it's referenced down the bottom for  
3 you -- is I intended to point out to you that if  
4 you give a full-agonist opioid like methadone,  
5 morphine, tapentadol, oxycodone, oxymorphone,  
6 whatever it happens to be, the more you give, the  
7 more activity you get, and the more toxicity you  
8 get.  
9 If you give a partial agonist like  
10 buprenorphine, there's a plateau effect not only in  
11 the analgesic efficacy, but also in the toxicity,  
12 at least to some extent. For example, you won't  
13 continue to get CO<sub>2</sub> accumulation as the  
14 buprenorphine dose goes up, but that will happen  
15 with full-agonist opioids. Then, of course, if you  
16 give an antagonist like naloxone or naltrexone, you  
17 get no effect on respiratory response. So that's  
18 sort of an easy way to compare some of these drugs.  
19 This slide I title, A Rose By Any Other  
20 Name. We have different acronyms that we use for  
21 these morphine equivalents. We have morphine  
22 equivalent daily dose; we have DDD, defined daily

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1 dose; OMEQ, oral morphine equivalent dose; and  
2 MEDD, morphine equivalent daily dose.  
3 They essentially all mean the same thing.  
4 But maybe, just maybe, what we need is not so  
5 much -- let me see if it's on this slide or not.  
6 Maybe what we need is a morphine analgesic  
7 equivalent, if that's even possible, or a morphine  
8 toxic equivalent. And, really, the only way to do  
9 that, because of patient variability, would really  
10 be to be measuring O<sub>2</sub> levels, or CO<sub>2</sub> levels, in the  
11 patient.  
12 So it's really an impossible task unless we  
13 start using smartphones and technology in order to  
14 monitor these patients. It's not just a simple  
15 matter of math because not every opioid is the same  
16 and not every person is the same.  
17 Here in the next slide we talk about  
18 mu receptor binding affinity versus the partition  
19 coefficient. The partition coefficient really  
20 refers to the concentration ratio of the un-ionized  
21 compound, which is different from a distribution  
22 coefficient, which on this chart, distribution

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1 coefficient refers to the concentration ratio of  
2 all the species of the compound -- let's say it's  
3 morphine -- whether it's ionized or not ionized.  
4 The purpose of this slide, without getting  
5 into too much math, is to point out -- look on the  
6 top. Sufentanil has the smallest K value. The  
7 lower the K value, the higher the binding affinity  
8 to the mu receptor in the central nervous system.  
9 Sufentanil has a very, very high binding affinity  
10 to that mu receptor.  
11 Look at buprenorphine, which is a partial  
12 agonist, and of course not only used for pain  
13 management but for opioid-use disorder. It has a  
14 similar binding affinity. In fact, its binding  
15 affinity to a mu receptor is higher than all the  
16 drugs below it.  
17 Then if we look at, for example, morphine  
18 and fentanyl, we all know that fentanyl is a very  
19 potent opioid, but if we look at morphine and  
20 fentanyl that are highlighted there for you, they  
21 have a similar binding affinity to the receptor  
22 once they get to the receptor. That's very

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1 important; once they get to the receptor. They  
2 have to get there.  
3 The next column is the partition  
4 coefficient. The partition coefficient, again, is  
5 the concentration ratio of an un-ionized compound.  
6 You see that fentanyl has a very high partition  
7 coefficient, and in this case, the higher the  
8 number, the more easily the drug gets into the CNS.  
9 Look at buprenorphine. It has a higher  
10 partition coefficient than sufentanil, and as we go  
11 down, you see these various other ones. Morphine  
12 is actually pretty low, but fentanyl has a  
13 partition coefficient somewhere between sufentanil  
14 and buprenorphine.  
15 So again, to think that we can do a simple  
16 equation of morphine to another opioid is just  
17 wrong. It has to do with the binding affinity to  
18 the receptor and how quickly the drug gets into the  
19 CNS.  
20 Molecular weight is not quite as important  
21 in discussion here, but it's included in this  
22 chart. Then the last column, equivalent



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1 equianalgesic IM dose, now we're not talking oral  
2 to oral, but we're talking injectable. You can see  
3 there that sufentanil is up to a thousand times  
4 more potent than morphine, and buprenorphine is  
5 40 times more potent than morphine. In fact, there  
6 are some studies that show as an analgesic,  
7 buprenorphine sometimes acts as a full agonist in  
8 terms of analgesia. This is just to point out that  
9 complexity, from a physicochemical standpoint, are  
10 some of the disparities.

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

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

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

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

10 If you look over at methadone, we have  
11 111 plus or minus, so that's 222. Right? And you  
12 look, and 186 -- and I separate this by people that  
13 are trained in pain management, in palliative care,  
14 and none of the above. This is problematic because  
15 even if we make guidelines and we leave it to the  
16 clinicians, the clinicians do not all agree on what  
17 and opioid equivalent is.

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

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1 that we have quite a variability.

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

9 Again, patients were either underdosed by  
10 55 percent or overdosed by 242 percent. And look  
11 at the two drugs there that had the highest risk.  
12 They are fentanyl and methadone. That's a problem;  
13 obviously, that's a problem. I showed you on the  
14 previous slide that fentanyl and methadone were  
15 outliers in terms of what people thought were their  
16 conversions. Now, whether they used the opioid  
17 conversion calculator or they did it in their head,  
18 I don't know. But the point is that fentanyl and  
19 methadone are particularly dangerous here.

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

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

7 Ayonrinde came along in 2000 and said, well,  
8 if 3 points are good, then 6 points must be better,  
9 so he did the same type of thing and gave us these  
10 conversion ratios. Then Mercadante in 2001  
11 published a paper, and if you compare Mercadante to  
12 Ripamonti, you'll see 3.7 was just rounded to 4;  
13 7.75 was rounded to 8; and 12.25 was rounded to 12.

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

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

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

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

15 But look at Ayonrinde's, and that was the  
16 6 data point one. In Ayonrinde's, that one data  
17 point that I circled, 300 milligrams of morphine  
18 equals 60 milligrams of methadone, but  
19 302 milligrams of morphine equals 30 milligrams of  
20 methadone. So imagine if you did that  
21 bidirectionally what a disaster that could be.  
22 Then the formula that I created is that dotted

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

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

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

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

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

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

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

15 Now, think about this. If we use a  
16 traditional opioid conversion, a 25-microgram patch  
17 is equivalent to 22 and a half to 60 some odd  
18 milligrams of oxycodone, so let's say  
19 40 milligrams. So 40 milligrams times 4, we're  
20 talking about 160 milligrams of oxycodone would  
21 have been the conversion. And even if we reduce  
22 that by 50 percent, which the FDA I believe

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1 recommends, we still would have overdosed this  
2 patient.

3 So it turns out that the serum levels came  
4 back to be around let's say 3 nanograms per mL,  
5 which is -- no, actually it was even less than  
6 that. The patient had blood levels that were  
7 equivalent to a 12.5-microgram patch, which is  
8 20 milligrams of oxycodone, so we cannot predict  
9 this, particularly in cachectic patients.

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

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

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1 3A4 to its inactive form, and oxycodone is also  
2 metabolized by 3A4 to its inactive form.  
3 There are basically two bridges out. You  
4 think of getting out of New York City. There are  
5 only so many bridges out. So oxycodone, you get  
6 metabolized to its active form, which some people  
7 say oxymorphone is twice as potent as  
8 oxycodone -- maybe, maybe not -- but 3A4  
9 metabolizes it to noroxycodone.  
10 What would happen if those things were shut  
11 down or the bridges opened up, and it was very easy  
12 for them to convert? We're going to come back to  
13 that when we talk about pharmacogenetics.  
14 Medication metabolism is important. Phase 1  
15 metabolism involves the cytochrome or CYP. They're  
16 listed there for you, and the drugs on the  
17 right-top row are drugs that do require CYP  
18 metabolism.  
19 For phase 2, they don't require CYP  
20 metabolism. They're easier to metabolize. You can  
21 see on the right side there that morphine,  
22 oxymorphone, hydromorphone, and tapentadol do not

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1 require CYP metabolism. We can also add  
2 levorphanol to that list.  
3 Why is this important? It is extremely  
4 important because, as I told you on the last slide,  
5 oxycodone is metabolized -- and I'm going to go  
6 back -- by 2D6 to oxymorphone and 3A4 to  
7 noroxycodone, which is inactive. What if a  
8 patient was an ultra-rapid metabolizer of 2D6 and  
9 rapidly converted oxycodone to oxymorphone, which  
10 is more potent, and they were also a poor  
11 metabolizer of CYP3A4 -- I'm sorry, a rapid  
12 metabolizer -- no. Lets' say they're a poor  
13 metabolizer of CYP3A4, so they're getting activity  
14 from oxymorphone and oxycodone.  
15 Now, what if the patient was an ultra-rapid  
16 3A4 metabolizer, so they're rapidly metabolizing  
17 oxycodone to noroxycodone, which is inactive, and  
18 they're a poor 2D6 metabolizer? So they're not  
19 converting any oxycodone to oxymorphone.  
20 Basically, they will be able to tolerate a much  
21 higher dose of oxycodone because the active drug is  
22 not going to stay around long. Alright?

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1 Now, the patient, all of a sudden they're on  
2 OxyContin, or Xtampza, or whatever extended-release  
3 oxycodone they are, and then they have to change  
4 insurance companies, and the insurance company  
5 says, "I'm sorry. We don't cover extended-release  
6 oxycodone. You'll have to change the patient to  
7 extended-release morphine," and so you do that.  
8 Oh-oh. We have a big problem here because if you  
9 use the math to do it, you're not considering the  
10 patient's pharmacogenetics. Morphine does not rely  
11 on CYP metabolism. You will overdose that patient.  
12 Now, if we go back and the opposite happens,  
13 that the patient's an ultra-rapid 2D6 metabolizer  
14 and they're a poor 3A4 metabolizer, then that's a  
15 situation where they would require a lower dose.  
16 In that case, if you change with the morphine,  
17 you're going to underdose them.  
18 Summarizing on this next slide, genetic  
19 variability is important. Forty to 60 percent of  
20 patients do have this phenotype variability of  
21 being different kind of metabolizers. The most  
22 common CYP enzymes are listed there for you. Of

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1 those enzymes, 3A4 is the most common. This is not  
2 just for analgesics, but for all drugs that go to  
3 the CYP system, about 85 percent of them are  
4 CYP3A4.  
5 So we cannot just do simple math. We have  
6 to think about pharmacokinetics. We have to think  
7 about pharmacodynamics and how the drug actually  
8 works. I gave you examples of certain drugs that  
9 have more of an effect, perhaps, on neuropathic  
10 radicular pain, things like tramadol, tapentadol,  
11 methadone, and levorphanol, and then of course  
12 pharmacogenetics.  
13 So what does this CYP thing all mean? Just  
14 to make it clear for everybody here, because a lot  
15 of people throw around this term "CYP" or  
16 "cytochrome" and we're not really sure what it  
17 means, the first number is the identifying enzyme  
18 family, the letter is the subfamily, and the last  
19 number, believe it or not, is the order in which it  
20 was discovered; kind of crazy, but that's what it  
21 is.  
22 What about drug interactions? Certain drugs

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1 can make the liver turn out more enzymes, more of  
2 those CYP enzymes. Those drugs are inducers. A  
3 great example of that is carbamazepine. It induces  
4 certain CYP enzymes.  
5 Then there are other drugs that are  
6 inhibitors, things like erythromycin,  
7 clarithromycin. They inhibit 3A4. That would be  
8 quite dangerous in the patient on oxycodone. Then  
9 the drug that gets metabolized by the CYP enzyme is  
10 the substrate, and polymorphism is the genetic  
11 variability among a population, how different  
12 people have different enzymes. For example, in  
13 Japan, they have more 2D6 than Caucasians do, and  
14 as you travel around the globe, you can actually  
15 map out the enzymes and the populations change as  
16 you go around the globe.  
17 How do we personalize these things and what  
18 are the other issues? This next slide talks about  
19 P-glycoprotein, and unfortunately, P-glycoprotein  
20 interactions are often not included in a lot of the  
21 pharmacy software packages. That's problematic.  
22 I know I don't have time to go through all

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1 of these, but I'm going to give you an example,  
2 example number two, in a paper that our group  
3 published here up in Albany, where a patient was  
4 coming into the hospital and had endocarditis.  
5 The patient was home on pretty good doses of  
6 oral morphine, but because of the endocarditis was  
7 also being treated with rifampin. Well, rifampin  
8 is a P-glycoprotein inducer. Morphine relies very  
9 heavily on P-glycoprotein to pull it back into the  
10 gut, so it's kind of a protective mechanism.  
11 If the P-glycoprotein is elevated, then that  
12 means that less morphine is going to be absorbed.  
13 So imagine if this patient comes into the hospital  
14 and we're going to set them up for heart surgery  
15 and put them on IV morphine, they will be overdosed  
16 because IV morphine is not the same as PO morphine.  
17 PO morphine depends on P-glycoprotein.  
18 P-glycoprotein is a protective mechanism to pull  
19 drugs back into the gut so they don't get absorbed.  
20 That's also an important consideration. A  
21 number of drugs either induce or inhibit  
22 P-glycoprotein, and also there are pharmacogenetic

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1 differences in P-glycoprotein amongst patients.  
2 P-glycoprotein also varies in the CNS and is  
3 important for carrying certain opioids across the  
4 blood-brain barrier.  
5 What are the phenotypes? There's wild-wild,  
6 variant-wild, and wild-variant. You get an allele  
7 from the mother and from the father. If both have  
8 the wild gene, then you're considered a normal  
9 metabolizer, which is termed "extensive  
10 metabolizer." If you're a variant-wild or a  
11 wild-variant, so one parent is the variant and one  
12 has the wild gene and vice versa, then you could  
13 probably be an intermediate metabolizer. But if  
14 you're a variant and variant, then you're more  
15 likely to be an ultra-poor or ultra-rapid  
16 metabolizer.  
17 This shows you what the difference is The  
18 first one shows if you're a poor metabolizer,  
19 you're not going to get as much metabolite, keeping  
20 in mind, again, that some of the metabolites are  
21 active and sometimes they're inactive.  
22 Intermediate metabolizer, you see a picture of

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1 that; extensive metabolizer, which would be normal,  
2 and ultra-rapid metabolizer. I'm showing you large  
3 M's and small M's for the different metabolites.  
4 I'm going to go through a couple of cases  
5 really quickly to finish this up, and these are  
6 real cases.  
7 JB is a 45-year-old Caucasian male who has a  
8 history of cervical stenosis at C5-C6 with  
9 myelopathy. He has been on tramadol for a number  
10 of years, but he comes to you for assistance with  
11 optimal control of neuropathic pain. You initiate  
12 carbamazepine 100 milligrams PO daily for 7 days,  
13 then 200 milligrams daily. Three weeks later, JB  
14 calls the clinic in distress. He reports being in  
15 the worst pain he has experienced in years.  
16 Why is he suddenly in pain? He's in pain  
17 because it takes about 3 weeks for enzyme induction  
18 to happen. What happened is not only is tramadol a  
19 substrate for CYP3A4, carbamazepine induces 3A4,  
20 but carbamazepine is also an autoinducer. Not only  
21 does it increase CYP3A4 enzymes, but it itself is  
22 metabolized by 3A4. So not only did the tramadol

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1 levels go down in this patient, but so did the  
2 carbamazepine levels.  
3 I think it's also extremely important to  
4 point out here that although induction, or having  
5 the liver put out more enzymes, takes 3 weeks,  
6 inhibition -- so a drug that inhibits an enzyme  
7 like erythromycin or clarithromycin -- only takes  
8 48 hours, so that could be a disaster.  
9 Here's a case, RC. The patient is a  
10 48-year-old male with a past medical history  
11 significant for ADHD, OSA, PTSD, and chronic low  
12 back pain. The pain level on a visual analog scale  
13 of 0 to 10 was 9 out of 10. He was intolerant to  
14 many antidepressants: duloxetine, venlafaxine,  
15 citalopram, sertraline, bupropion, and mirtazapine.  
16 He had a mild response to morphine.  
17 When we tested him pharmacogenetically, he  
18 had reduced activity for COMT. Now, that would  
19 actually, for neuropathic pain, be a good thing for  
20 him because COMT, catechol-o-methyl transferase, is  
21 an enzyme that breaks down the neuroamines of the  
22 synaptic space, so if he had reduced activity, he

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1 had more amines there. MTHFR, methylene-  
2 tetrahydrofolate reductase, reduced activity;  
3 3A4-3A5 intermediate metabolizer, not usually too  
4 much of a problem; and the others were normal.  
5 What about MTHFR? Well, MTHFR is important  
6 in treating depression. I don't care how many  
7 antidepressants you give to a patient, they are not  
8 going to work if you don't have the capability of  
9 converting folic acid to tetrahydrofolate acid.  
10 That's what MTHFR does. You need to have the  
11 active form.  
12 So we treated this patient with  
13 L-methylfolate -- oh, no. You have a choice  
14 between L-methylfolate or leucovorin. The VA does  
15 not like using L-methylfolate because it's a  
16 natural substance, so I was forced to prescribe  
17 leucovorin or folic acid. That, unfortunately,  
18 reduces zinc, so we supplemented the patient with  
19 zinc, and 8 months later this patient was stable,  
20 required absolutely no opioids at all, didn't need  
21 anything for ADHD, and was a changed person. We  
22 published this case study, and it's referenced

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1 number 2 for you.  
2 Patient SR, 47-year-old female patient with  
3 3 failed back surgeries; diabetic type 2; 5'6",  
4 weighs 200 pounds; medication regimen for the last  
5 2 years, no changes; urine screen is good, no  
6 problems; 30 milligrams oxycodone continuous  
7 release every 12 hours; oxycodone IR 10 milligrams  
8 q4h PRN, usually took 2 or 3 a day.  
9 Do you think that this patient is an  
10 elevated risk? Most people say low-to-moderate  
11 risk, and that I think on the face is probably  
12 true. Patient's tolerance to these opioids, doing  
13 well, being closely monitored.  
14 But here's what we don't know. Medications  
15 prescribed by a psychiatrist include lorazepam  
16 every 8 hours for anxiety. Thankfully now, PDMPs  
17 are shared amongst most states. But what if the  
18 patient is placed on pregabalin 75 PO TID by the  
19 endocrinologist for diabetic peripheral neuropathy?  
20 Then the patient decides to go on a  
21 grapefruit diet, which inhibits CYP3A4, and  
22 unbeknownst to us, the patient's an ultra-rapid 2D6

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1 metabolizer and they're converting oxycodone to  
2 oxymorphone. How do we know that if we didn't do a  
3 genetics test?  
4 Patient develops an upper respiratory tract  
5 infection, which in and of itself is a problem, and  
6 then the patient decides to go to the pharmacy and  
7 pick up some Benylin cough syrup, which is Benadryl  
8 or diphenhydramine. We have a problem. Now the  
9 patient goes from low-to-moderate risk to a very,  
10 very high risk.  
11 This is my last wrap-up slide here,  
12 Transforming Negative Perception in a Perfect  
13 World. There are problems, as was pointed out in  
14 the first couple of lectures this morning. What  
15 opioids are really killing our community and how?  
16 We need to be very cognizant of the fact that  
17 fentanyl is not the same as these fentalogues, or  
18 these fentanyl analogues, on the street. And I  
19 think that it behooves all of us, whether it's the  
20 regulatory agencies or responsible reporting in  
21 mainstream media, that pharmaceutical fentanyl is  
22 not the same as these fentanyl analogues on the

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1 street.

2 Secondly, community and patients, we need to

3 educate and seek education from medical providers

4 and from pharmacists. We need, I think, to support

5 pharmacy provider status. I've heard several times

6 this morning already that practitioners don't have

7 enough time to see these patients. They had all

8 the education to see these patients, to have the

9 wherewithal to make some of the decisions that are

10 required to be made, that will be made maybe in a

11 specialty clinic.

12 There are pharmacists who are two years

13 post doctorate, do pain and palliative care

14 residencies, and who are stars in this area.

15 Pharmacists can prescribe nationwide in almost all

16 states in collaboration with physicians, but they

17 are not paid by insurance carriers to see patients,

18 and they could really help to mitigate these risks.

19 But for some God unknown reason, Congress has not

20 seen fit to make pharmacists providers, as pretty

21 much all other clinicians that see patients are

22 considered providers and are paid for it, but

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1 pharmacists are not.

2 So in closing, I'd like to ask everybody

3 here to support provider status for pharmacists,

4 and that is my presentation. Thank you very much

5 for inviting me. Thank you to Grace and the whole

6 team.

7 DR. CHAI: Thank you, Dr. Fudin. That was a

8 very complex presentation, and it's really building

9 upon the science that we are trying to share here

10 at this workshop, and thank you for getting us back

11 on track.

12 We will now hear from three speakers from

13 the Veterans Health Administration, Dr. Friedhelm,

14 Dr. Emmendorfer, and Dr. Cunningham.

15 Please take it away. Thank you.

16 Presentation

17 Friedhelm Sandbrink and Thomas Emmendorfer

18 DR. SANDBRINK: Good morning. I'm going to

19 get started. I'm Friedhelm Sandbrink, and thank

20 you, Dr. Chai and the FDA, for organizing this

21 meeting and giving us the opportunity to talk about

22 Opioid Prescribing and the Opioid Safety Initiative

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1 in the Veterans Health Administration.

2 These are our standard disclosures.

3 Obviously, these are our personal opinions and do

4 not reflect the official views of the Department of

5 the Veterans Affairs or any federal agencies.

6 I will get started with an overview about

7 pain management and opioid safety in veterans

8 receiving care in the VHA, and then together with

9 Dr. Emmendorfer, we will talk about the Opioid

10 Safety Initiative specifically, and opioid

11 prescribing, and opioid risk mitigation. The third

12 section will be by Dr. Cunningham about a

13 deprescribing and tapering assessment that we did

14 among veterans who discontinued opioid as part of a

15 medication-use evaluation.

16 As a background, out of the 20 million

17 veterans who we see and who are in the United

18 States, about 9.7 million have contact, whether

19 it's benefits or healthcare, with the VA, and about

20 6 million really receive health care, including

21 primary care.

22 When we look at the assessment of what is

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1 the prevalence of pain in veterans in the United

2 States, in general -- and this is not all of United

3 States -- I'm showing here the data from the

4 National Health Interview Survey in 2016 that

5 specifically talked about the subset of patients

6 who have severe pain, and that's 9.1 percent in

7 veterans that was 40 percent more common than the

8 non- veteran population.

9 These are mostly musculoskeletal pain

10 conditions. But if you look at this over on the

11 right side -- this is stratification according to

12 age -- you will see that blue are the columns for

13 the prevalence in veterans. And even at a younger

14 age, really across the board, the number of

15 veterans who have high-impact pain, have severe

16 pain, is significant, and it centers around the

17 8 to 10 percent range.

18 When we look at the 6 million veterans in

19 the VA who receive their care within primary care,

20 2 million have a pain diagnosis, but it's only

21 120,000 in this analysis from 2012 that get seen in

22 the pain clinic. So when we make guidance for pain

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1 management, we always have to keep the primary care  
2 in mind and the general care that we provide.  
3 Again, this analysis, also about internal VA  
4 veterans, shows that 1 in 10 had severe persistent  
5 pain. But this analysis of those patients who had  
6 severe pain who attended the pain clinic shows that  
7 mental health conditions really is what separates  
8 those patients who have severe and persistent pain.  
9 This is in regard to our overall prescribing  
10 and implementation of multimodal pain care. This  
11 is a study that only goes to 2015, but as you can  
12 see here, on the right side in the graph in the  
13 violet-purple and the light green, that is opioid  
14 prescribing, and specifically in the light green is  
15 the long-term opioid therapy.  
16 Those numbers have been trending down  
17 steadily since 2010 already, whereas others, which  
18 here is access to physical therapy and opioid  
19 therapy and behavioral health care, have  
20 significantly increased.  
21 When we look at the risk, though, of  
22 veterans in the Veterans Health Administration in

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1 regard to opioid overdose and in regard to  
2 suicides, we know from our epidemiological data  
3 that the mortality rate for opioid overdose is  
4 about 1.5 times greater in VHA veterans than in the  
5 general U.S. population. This analysis here looked  
6 at 2016 data where there were 1,271 deaths of VHA  
7 veterans from an opioid overdose. That's about  
8 3 to 4 veterans a day.  
9 We also realize that the suicide rate is  
10 about 1.5 times greater in VHA veterans than in the  
11 general U.S. population. We note that pain is the  
12 most common factor among veterans who die by  
13 suicide, and we heard this also from Penney Cowan  
14 earlier today, that opioid prescribing, and  
15 especially deprescribing, and opioid  
16 discontinuations, abrupt discontinuations, are at  
17 least anecdotally reported to be connected with  
18 suicide risk or suicide attempts.  
19 The bottom line, though, is that we have to  
20 integrate the mental health assessment and the  
21 treatment of mental health factors into our pain  
22 care.

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1 There are other studies obviously not just  
2 for veterans, but we have several studies looking  
3 at the risk of opioid overdose correlated to the  
4 opioid dosage and morphine milligram equivalent and  
5 MMEs.  
6 This is Dr. Bohner's study here in blue that  
7 shows obviously that the higher the dosage is, the  
8 higher the risk is for an unintentional overdose.  
9 The increase with dosage in regard to risk of  
10 suicide is also there, but the factor is certainly  
11 smaller. It's about a factor of 2 times for  
12 suicide risk at 100 milligrams or higher of  
13 morphine equivalent versus a factor of 7 times  
14 higher in this study for unintentional overdose.  
15 We do have to realize that these are  
16 correlations that are being noted, but it doesn't  
17 mean that that's the opioid prescribing in itself.  
18 It may be the mental health factors that lead to  
19 severe pain and opioid prescribing in itself that  
20 actually drives suicide risk.  
21 We did an analysis recently looking at data  
22 from 2013, looking at every patient in the VA

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1 system who was on opioid medication, and followed  
2 them up to the end of 2014 in regard to what were  
3 the factors and what were the characteristics of  
4 those patients who had a mortality from an overdose  
5 or from suicide.  
6 This is comprehensive observational data  
7 that we did in the VA system, but as you can see  
8 here, the dosage, the most common dosage of  
9 patients who die of an overdose or suicide is in  
10 the lower dosage range. It's 20 to 50 milligrams  
11 morphine equivalent because the vast majority of  
12 patients who are on opioid medication long term are  
13 on these kinds of dosages.  
14 If you just concentrated on the high-dose  
15 opioid therapy patients, if I take the definition  
16 of more than 90 milligrams of MME, that would  
17 capture only about 20 percent of all patients who  
18 in 2013 were on such a dosage or on an opioid  
19 medication and then had a death from a suicide or  
20 an overdose by the end of 2014.  
21 Four out of 5 patients had dosages below  
22 the 90 milligrams of morphine equivalent; 3 out of

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1 4 opioid overdose patients or suicide deaths were  
2 among patients who had a mental health or substance  
3 abuse diagnosis; and in red here are the mental  
4 health diagnoses; other; then blue is the SUD  
5 diagnosis.  
6 So with this, I'm going to lead over now  
7 towards our Opioid Safety Initiative in the VA  
8 system. That was piloted in 2012 and then expanded  
9 nationally in 2015. Clearly, the Opioid Safety  
10 Initiative aim included, obviously, a reduction of  
11 the overreliance on opioid analgesic medication for  
12 pain management when it may not actually be needed,  
13 and at the same time to make opioid prescribing and  
14 opioid therapy more safe and also more effective  
15 than actually clinically indicated.  
16 We developed an OSI dashboard. PBM  
17 developed that together with other stakeholders to  
18 make the total opioid prescribing visible within  
19 the VA system. But we also realized very early on  
20 that what we needed was a comprehensive strategy,  
21 like an opioid stewardship initiative across the VA  
22 system that also takes in provider education and

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1 broadens access to non-pharmacological modalities,  
2 because the goal is, of course, better pain care  
3 and better improvement in regard to the management  
4 of pain, and better function of our veterans.  
5 So we had to make sure to include and expand  
6 the access in regard to behavioral and CIH  
7 modalities, as well as physical therapy modalities  
8 and other restorative and interventional providers.  
9 Specifically, we included the development of an  
10 academic detailing service within the VA system for  
11 provider education but also for patient education.  
12 I'm just going to show you two slides about  
13 our VA/DoD Clinical Practice Guideline for opioid  
14 therapy that was published in 2017; clearly, a very  
15 important component of our Opioid Safety  
16 Initiative. It does have 18 recommendations. Many  
17 of them are very much aligned to the CDC  
18 recommendations established shortly before the  
19 VA/DoD Clinical Practice Guideline, but there are a  
20 few nuances, just a few differences.  
21 One, obviously, is that we actually made a  
22 recommendation against -- and this is here that I

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1 want to emphasize -- initiation of long-term opioid  
2 therapy. We didn't say make a recommendation  
3 against patients on long-term opioid therapy  
4 already on there. We also didn't say that you  
5 shouldn't prescribe opioids when they're clinically  
6 indicated in particulars such as for short-term  
7 use. But we felt that there were really data out  
8 there that suggested that a general recommendation  
9 against initiation of long-term opioid therapy as a  
10 guidance, the guideline document was appropriate.  
11 The second component that we did in this  
12 clinical practice guideline is that we said that  
13 opioid dosage reductions must be individualized to  
14 the patient. We specifically issued caution  
15 against sudden reductions; indicated that opioid  
16 tapering, if it is being pursued for risk greater  
17 than benefit, has to be done very slowly.  
18 (Background noise.)  
19 DR. SANDBRINK: If everybody can mute their  
20 phone.  
21 DR. CHAI: We'll pause here.  
22 Could everyone please mute their phone?

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1 DR. SANDBRINK: Thank you.  
2 DR. CHAI: Thank you.  
3 DR. SANDBRINK: So we did make caution  
4 against sudden or fast discontinuations of opioid  
5 medication, and obviously included risk about  
6 opioid-use disorder and the availability of access  
7 to treatment for patients who may be affected by  
8 that.  
9 So with this, I will hand it over to  
10 Dr. Emmendorfer, who will tell you more about our  
11 Opioid Safety Initiative and risk mitigation  
12 factors that we've been implementing.  
13 Tom, can you take over?  
14 (No response.)  
15 DR. CHAI: Dr. Emmendorfer, should we try to  
16 pull you up on audio? Are you able to hear us?  
17 Can you chat?  
18 DR. SANDBRINK: So while we're waiting for  
19 Dr. Emmendorfer to come on, I can maybe get started  
20 with presenting the first part of his slides. And,  
21 Tom, whenever you're on let us know, and you can  
22 take this over.



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1 DR. CHAI: Thank you, Friedhelm.  
2 DR. SANDBRINK: Oh, wonderful.  
3 (Pause.)  
4 DR. CHAI: Would you like to try to present  
5 a few of the slides for Dr. Emmendorfer until we're  
6 able to get him on?  
7 DR. SANDBRINK: Yes, I'd be happy to do  
8 that.  
9 DR. CHAI: Okay. Thank you.  
10 DR. SANDBRINK: Alright. I already  
11 mentioned that we have this Opioid Safety  
12 Initiative dashboard that we established to make  
13 the opioid prescribing visible across the system.  
14 DR. EMMENDORFER: Can everybody hear me now?  
15 I just disconnected from the phone and tried  
16 through the laptop.  
17 DR. SANDBRINK: Yes, we can hear you now.  
18 Tom, please, go ahead. Tom, we can hear  
19 you.  
20 (Pause.)  
21 DR. SANDBRINK: Could hear you.  
22 (Pause.)

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1 DR. SANDBRINK: Alright. Tom, let us know  
2 when you are on.  
3 The Opioid Safety Initiative dashboard  
4 included information -- and it does and continues  
5 to include -- about total opioid prescribing,  
6 specifically about opioid and benzodiazepine  
7 co-prescribing, and then the high-dose opioid  
8 prescribing.  
9 In the past, we defined it as greater than  
10 100 milligrams of MME. Now we are defining, and we  
11 have adopted the more general standard of  
12 90 milligrams of morphine equivalent, and we've  
13 back-calculated our dashboard accordingly.  
14 We also will show you data about long-term  
15 opioid prescribing and implementation of risk  
16 mitigation strategies, in particular urine drug  
17 screens, and the other parameters that are listed  
18 here. We will show you some of the information  
19 about these parameters. They include, obviously,  
20 an informed consent.  
21 Tom, are you on?  
22 DR. EMMENDORFER: I'm on, Friedhelm.

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

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

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

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

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

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

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1 concerns that patients have and may have, and we  
2 got opioid dosage reduction, encouraging  
3 discussions and a conversation about what the goals  
4 of treatment are, taking any concerns into  
5 consideration and having patient-centered decision  
6 making in regard to the next steps.  
7 In 2016 and '17, or 2016 already, we did  
8 recommend that if a provider and the patient are  
9 pursuing an opioid dosage reduction that, in  
10 general, the reduction should be very slow. We  
11 mentioned 5 to 20 percent every 4 weeks at that  
12 time as a suggestion, so it's about 10 percent a  
13 month.  
14 Realizing that there was no clear data in  
15 the literature to suggest a specific number, we did  
16 not put a specific number as a recommendation into  
17 our clinical practice guideline, but taking these  
18 concerns into account, we've streamlined our opioid  
19 taper decision support tool for our providers  
20 accordingly.  
21 I want to mention this tool that we  
22 developed in the VA system. It's called the

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1 Stratification Tool for Opioid Risk Mitigation.  
2 STORM is how it's commonly known. It takes  
3 individual patient factors into account to really  
4 develop a predictive analytic estimate of what the  
5 risk is for an overdose or suicide in the next year  
6 and in the next three years.  
7 So it really gives you a score, a risk  
8 score, that is based on the patient's  
9 individualized factors and allows really meaningful  
10 discussions with the patient about what the  
11 concerns are. But also the STORM dashboard  
12 highlights what risk mitigation strategies can be  
13 still implemented to make care possibly safer.  
14 We've used STORM, this dashboard, now to  
15 establish at every VA facility a team, a STORM risk  
16 review team that takes these database risk reviews  
17 and makes recommendations for the care of those  
18 patients that are identified as very high risk.  
19 Our first data clearly shows that this  
20 approach actually is saving lives, and we've made  
21 care for our veterans safer, and that providers  
22 take this guidance that they receive into account

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1 to make decisions with our patients and to support  
2 them.  
3 There was one observational study that I  
4 briefly mentioned already. I just want to show the  
5 slide from this. It's an observational study that  
6 looked at those patients, from 2013 and looked at  
7 the probability of a death from that overdose or  
8 suicide, treated with this opioid in 2013, after  
9 stopping opioid medication, in correlation to how  
10 long patients had been on opioids before.  
11 You can see these four lines here on the  
12 graph, and the dashed blue line, that's previously  
13 treated for more than 400 days. So really, on  
14 long-term opioid therapy, you can see that, in  
15 particular, the higher the dosage, the higher the  
16 risk after the opioid stoppage, after the last  
17 opioid prescription has happened for a death, of an  
18 outcome of a death.  
19 The correlation, in particular in the first  
20 25 days, is very high. We took this to guide our  
21 providers to truly mitigate risk if, out of  
22 whatever reason, opioid medication is being

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1 stopped, and for the next 3 months after starting  
2 or stopping opioid medication, that the support is  
3 intensified and there's ongoing communication and  
4 interaction with the patient.  
5 Also, part of what we do in these opioid  
6 risk reviews is we look for patients who may have  
7 opioid-use disorder to make sure that we provide  
8 access to MOUD, medication opioid-use disorder.  
9 Specifically, pain clinics and primary care clinics  
10 are included in what we call level one,  
11 addiction-focused medical management that we  
12 integrate where patients and providers are.  
13 We're realizing that patients may be at risk  
14 for being identified as having abnormalities or  
15 irregularities in regard to their opioid  
16 prescribing and when the opioid is discontinued,  
17 and there's clearly access integrated into all pain  
18 management teams to allow access to opioid-use  
19 disorder treatment if clinically indicated.  
20 With that, I will hand it now to  
21 Dr. Cunningham to talk specifically about our  
22 medication use evaluation.

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

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

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

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

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

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

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

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1 AFTERNOON SESSION  
2 (1:00 p.m.)  
3 DR. CHAI: If you have joined us back for  
4 the 1 p.m. mark, please give us a few more minutes.  
5 We're just working out a few Logistics. Thank you.  
6 (Pause.)  
7 DR. CHAI: Dr. Cunningham, is your audio  
8 connected.  
9 (No response.)  
10 DR. CHAI: While we're waiting for  
11 Dr. Cunningham --  
12 DR. CUNNINGHAM: I am on.  
13 DR. CHAI: Oh. Thank you.  
14 DR. CUNNINGHAM: Sorry. I just got on.  
15 DR. CHAI: No. That's wonderful. Thank you  
16 for your flexibility and patience.  
17 Just to orient everyone, thank you and  
18 welcome back from lunch. We've changed the agenda  
19 a bit, but we'll finish hearing from our VA  
20 presenters, and then move on to a clarifying  
21 questions session.  
22 So we've reordered a bit to move lunch

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

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

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

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

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1 treatment plan and modes of therapy, it was better  
2 in fiscal year '17 than in fiscal year '13, and the  
3 pain improvement was also significantly better in  
4 fiscal year '17 than in fiscal year '13, and that's  
5 in the last box on the right-hand side.  
6 One of the other items we wanted to look at  
7 is monitoring activities, so we wanted to see if  
8 there are changes or improvement that occurred over  
9 time. The risk versus benefit improved in fiscal  
10 year '17, 59 percent versus 47 percent. It was  
11 significantly different.  
12 Then again, if you look at VA services  
13 during the tapering period, in fiscal year '13,  
14 behavioral sciences was greater than in fiscal  
15 year '17. But for the other pertinent areas,  
16 specifically pain management and pain clinic, CAM  
17 therapy and pharmacy consult, those were all  
18 greater in fiscal year '17 than in fiscal year '13,  
19 so that also began to improve over time.  
20 We looked at the modes of therapy, and looking at  
21 that, I think I went over that briefly earlier when  
22 I showed you that the modes of therapy improved

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1 between fiscal year '17 and fiscal year '13, so  
2 overall, we had an improvement of therapy.  
3 Our MUE showed that therapy definitely  
4 changed in regards to discontinuation and tapering  
5 methods. The MUE provided a comparison of opioid  
6 discontinuation and tapering methods and  
7 prescribing practices between the years of fiscal  
8 year '13 and '17.  
9 Although primary care was the main  
10 discipline, over the years we saw a  
11 multidisciplinary approach. As was described in  
12 the other slide, this was measured in these when we  
13 did the direct comparison between fiscal year '13  
14 and '17.  
15 Specifically, the high-dose opioid tapering  
16 plans were significantly longer compared to fiscal  
17 year '13 and were dynamically customized to the  
18 patient responses, which was definitely improvement  
19 over time. The final median opioid MEDD was  
20 significantly lower in fiscal year '17 prior to  
21 discontinuation when compared to fiscal year '13,  
22 and the pain management and improvement was

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1 significantly better compared to fiscal year '13.  
2 So all in all, we showed that our healthcare  
3 system was a learning healthcare system. We did  
4 see an improved response over time when we looked  
5 at the various responses in measurement between the  
6 two years.  
7 I'd like to wrap this up by just giving you  
8 some key resources that were used that you can  
9 identify when you're looking for our website in VA  
10 for pain management; for substance-use disorder;  
11 for OEND; academic detailing services; and also  
12 other items such as the DoD/VA Joint Pain Education  
13 Program, all listed here.  
14 Questions?  
15 DR. CHAI: Thank you, Dr. Cunningham, and  
16 thank you for your patience and flexibility during  
17 our extraordinary circumstances. We're all  
18 learning and doing really well, so thank you for  
19 that.  
20 DR. CUNNINGHAM: Okay. Thank you.  
21 Clarifying Questions to Speakers  
22 DR. CHAI: I appreciate a very comprehensive

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1 and insightful presentation from Dr. Sandbrink,  
2 Dr. Emmendorfer, and Dr. Cunningham. What we'll  
3 now do is our clarifying questions for the  
4 presentations you have heard today.  
5 We have divided the clarifying questions up  
6 into blocks so that we can try to handle as many as  
7 we can within our 15 minutes. What we'll ask you  
8 now to do is to please raise your hand. Use the  
9 raised icon -- and this is for all panelists and  
10 speakers -- to indicate that you have a question,  
11 and to remember to clear the icon after you have  
12 asked your question.  
13 When acknowledged, please remember to state  
14 your name before you speak and direct your question  
15 to a specific presenter, if you can. If you wish  
16 for a specific slide to be displayed, please let us  
17 know the slide number, if possible. Finally, it  
18 would be helpful to acknowledge the end of your  
19 question with a thank you and end your follow-up  
20 question with, "That is all for my questions," so  
21 we can move on to the next panel member.  
22 I understand there's been a lot of material

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1 covered, as well as many slides, so if you have a  
2 sense of which presentation and can describe the  
3 slide to some extent, we can try to find that for  
4 you. But what we ask is to please refrain from  
5 adjusting or moving the slide yourself because it  
6 will change the view for the entire audience. And  
7 with multiple people doing that at the same time,  
8 it will essentially become chaos. So what we're  
9 going to have is our AV team get us to any  
10 specific slide if we need to refer to it.  
11 So now at this time, we'd like to open it up  
12 for clarifying questions. I think we can start  
13 with Dr. Fine.  
14 Could you unmute your phone and state your  
15 name before you speak? Thank you.  
16 DR. FINE: Yes. This is Perry Fine. Are  
17 you able to hear me satisfactorily?  
18 DR. CHAI: Yes, very loud and clear.  
19 DR. FINE: Oh, very, very good. This is for  
20 Drs. McPherson and Fudin, who both just did an  
21 extraordinary job at summarizing the complexities  
22 of the issues, as well as recent science and

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1 scientific development in the last, say, decade.  
2 The question I have really dates back the  
3 last 10-15 years, looking at the Gammaitoni paper  
4 that Dr. McPherson cited, as well as a paper that  
5 was not cited but I think certainly deserves some  
6 acknowledgement. That is the Knotkova paper in  
7 2009, published in the Journal of Pain and Symptom  
8 Management, from research at Memorial Sloan  
9 Kettering and others, that looked at all the  
10 variables with regards to clinical application of  
11 dose equivalency or analgesic equivalency.  
12 At that point, it was pretty obvious that  
13 there was going to be no simple formula that was  
14 going to resolve all the clinical conundrums that  
15 had been raised.  
16 So my question has to do with, really, the  
17 more practical issue of, given the scientific  
18 developments, it's really not the science that is  
19 driving morbidity and mortality, or clinical  
20 applicability, or effectiveness and so on. It's  
21 really the acceptance and the ability to think  
22 through, as these two have succinctly said.

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1 It's really more of not so much education,  
2 but getting people to do the right thing, to  
3 actually apply what is known about these variables  
4 and to use the clinical skills and judgment that,  
5 as Lynn said, we all went to school for.  
6 Yet, I don't see that there's really much  
7 movement in the last ten years. And if we date  
8 back to the meeting we had at FDA in 2013, which  
9 would probably be useful to summarize at some point  
10 because that never really went very far, all the  
11 similar points were brought out, and yet eight  
12 years has gone by.  
13 So I'm asking these individuals, and anybody  
14 else who wants to participate in the discussion,  
15 how do we practically move forward? It seems to be  
16 independent from science and more a social  
17 phenomenon. Thank you.  
18 DR. McPHERSON: Well, Dr. Fudin, I can  
19 certainly take a crack at it. This is Lynn  
20 McPherson.  
21 Thank you, Dr. Fine. That's a great  
22 question. I wish I had a great answer for you. Of

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1 course, anybody who teaches at a professional  
2 school is going to have this opinion about their  
3 content. I happen to think that every medical  
4 school, pharmacy, nursing, and also social work and  
5 chaplaincy, should have content on primary  
6 palliative care skills, which certainly includes  
7 primary pain management skills.  
8 I think everyone should be -- I mean,  
9 everybody's going to die, and most people will have  
10 pain at some point in their life. So I think you  
11 have to start with education; what are the core  
12 minimum competencies, and then I think we have to  
13 hold these learners accountable in their  
14 experiential training as well so that it becomes  
15 incorporated into their practice. I mean, I'm not  
16 sure what else we can do. So those are my  
17 thoughts.  
18 DR. FUDIN: This is Jeff Fudin. I agree  
19 with Lynn. And, Perry, you bring up some  
20 incredibly interesting points. As everybody here  
21 knows, there's no easy answer. But I think that  
22 beyond the education -- and I said this, really, on



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1 my last slide -- I think that pharmacists are just  
2 terribly underutilized. Some of the people here  
3 that are not analysts, patients, and the like, may  
4 not understand the education and role of  
5 pharmacists.  
6 I think the government really needs to take  
7 a step to put pharmacists, really, in the limelight  
8 of what's going on here. We're talking about  
9 drugs. We're talking about pharmacogenetics,  
10 pharmacokinetics, and drug interactions. And there  
11 needs to be more collaboration not only between  
12 community pharmacists and their prescribers, but  
13 there needs to be more pharmacists in clinics, and  
14 they need to get paid for their work that they can  
15 and, in some instances, are already doing.  
16 It's not that we don't have the knowledge.  
17 Most of the people that are prescribing don't have  
18 extensive knowledge, but I think that globally as a  
19 medical society, including all healthcare  
20 providers, I think that pharmacists are often  
21 overlooked as part of that team, and they have a  
22 whole lot to offer, not only in a clinic setting

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1 and a community setting, but also in a hospital  
2 setting.  
3 I had a legal case where a patient was in  
4 the hospital on a stable dose of methadone for  
5 years, and he died in the hospital, and the  
6 presumption was that he was overdosed by giving a  
7 small dose of hydrocodone.  
8 What really happened is he had an infection.  
9 He was given moxifloxacin, which affects the  
10 QT interval, and he had an elevated QT interval for  
11 methadone. And as I mentioned in my lecture, it  
12 only takes 48 hours for that induction inhibition,  
13 and the guy died.  
14 So to me, I think it's really, really  
15 important -- and not for my own personal  
16 reasons -- that the government, all the  
17 agencies -- HHS, FDA, CDC, DEA -- really look at  
18 incorporating pharmacists more into direct patient  
19 care as a norm; not as an afterthought, which  
20 unfortunately it often times is.  
21 DR. CHAI: Thank you, Dr. Fudin.  
22 Just to orient everyone to this session,

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1 we'd like to keep it to clarifying questions, if  
2 possible. We are veering a bit into discussions  
3 that we hope to have tomorrow, so please keep your  
4 questions to clarifying questions, if possible.  
5 And please use the raised-hand icon, and I will  
6 call upon you to help organize this session.  
7 Dr. Bettinger, could you state your  
8 question, please?  
9 DR. BETTINGER: Yes. Hopefully this is a  
10 clarifying question. Hopefully, everyone can hear  
11 me ok here.  
12 This question is actually also directed more  
13 towards Dr. McPherson and Dr. Fudin, based around  
14 how to convert between different opioids. Both of  
15 you went over a lot of various scenarios of how to  
16 convert.  
17 I was just wondering -- and it could be  
18 helpful for especially all those listening  
19 today -- in particular for patients with chronic  
20 non-cancer pain who don't necessarily have access  
21 to really close monitoring, such as Dr. McPherson  
22 was talking about, palliative hospice care settings

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1 where nurses are integral every day or most days,  
2 what's the difference or what are some -- if you  
3 guys could clarify maybe between you -- specific  
4 recommendations that may differ in terms of the  
5 approach?  
6 After you calculate the opioid to convert  
7 to, what could be some of the approaches to get the  
8 patient to that conversion; again, thinking from a  
9 chronic non-cancer pain setting? Thank you.  
10 DR. FUDIN: This is Jeffrey, so I'll grab  
11 this one first.  
12 I think that, actually, consistent with some  
13 papers that both Dr. Perry fine did with Lynn  
14 Webster, I think that we should not be stopping the  
15 medications immediately, and it's because we cannot  
16 predict the equivalence exactly.  
17 So what I would do, I would begin to taper  
18 the drug that the patient is already on, maybe by  
19 even 50 percent, and then slowly introduce the new  
20 medication in an immediate-release dosage form  
21 slowly on a PRN basis, so that we can figure out  
22 what the tolerability is and what the needs are of

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1 that patient. Then it's going to be a matter of  
2 decreasing the original drug while slowly  
3 increasing the new drug.  
4 If the patient is on two medications, let's  
5 say extended-release morphine and let's say  
6 immediate-release hydrocodone, for example, what I  
7 would do there is I might cut the MS Contin dose in  
8 half, and I might start to escalate the hydrocodone  
9 dose if my intent was just to put the patient on  
10 hydrocodone.  
11 But if my intent was to put the patient on a  
12 fentanyl patch, well, then what I would probably do  
13 is reduce significantly the morphine dose. I would  
14 probably, again, use the hydrocodone for  
15 breakthrough pain. And when I got to a point that  
16 I felt safe, I would convert over to the fentanyl  
17 patch, and I would calculate it and then reduce it  
18 probably by 50 percent and use something for PRN.  
19 Hydrocodone would be a good choice because  
20 the patient was on that, or immediate-release  
21 morphine would be a good choice because the patient  
22 was already on morphine. But the point is do it

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1 slow and do it gradual.  
2 DR. CHAI: Thank you, Dr. Fudin.  
3 DR. MCPHERSON: If I could just add to that,  
4 I'm not as big of a fan of cross-tapering opioids  
5 because people tend to mess it up or they all of a  
6 sudden believe that they're a freelance pharmacist  
7 who can do this on their own, unless it's a  
8 crazy-crazy high dose of opioid you're converting  
9 from.  
10 But I would rather go with my golden rule,  
11 which is be very conservative with the standing  
12 schedule dose. And at least for the purposes of  
13 titration, even in a chronic non-cancer pain  
14 patient, to explain, and I think educating the  
15 patient that this is a partnership.  
16 I don't have a magic bean to say exactly  
17 where we're going to end up with this, so I need  
18 you to work with me on this. We're going to be  
19 liberal with the breakthrough for the next week  
20 until you can come back to clinic or whatever, so I  
21 need you to keep a good record for me, a medication  
22 administration record. I sometimes would even call

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1 the patient every day. You don't have to have a  
2 nurse go out, but I could call every day or every  
3 other day.  
4 So be conservative with the standing. I  
5 agree with Jeff about cutting back up to 50 percent  
6 as you're doing a conversion, and be, especially in  
7 the beginning, a little more liberal with the  
8 breakthrough, and still keep a close eye on them.  
9 That's all I have. Thank you.  
10 DR. CHAI: Thank you Dr. McPherson.  
11 What we'll have to do at this time to keep  
12 up with the schedule is to transition over to  
13 Dr. Zhang's presentation. I'm sorry for the abrupt  
14 transition, but it appears that we don't have any  
15 outstanding raised hands at this point.  
16 So thank you, Dr. McPherson and Dr. Fudin,  
17 for your responses to these questions.  
18 Dr. Zhang, are you ready to give your  
19 presentation?  
20 DR. ZHANG: Yes, I am. Can you hear me?  
21 DR. CHAI: Yes. Thank you.  
22 DR. ZHANG: Well, thank you so much.

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1 Presentation – Kun Zhang  
2 DR. ZHANG: Good afternoon. I hope  
3 everybody got recharged during their lunch break  
4 because what a great morning we had. I think all  
5 the presentations, including the opening remarks,  
6 are just excellent, as well as the discussion we  
7 just had. I really want to thank the team at FDA  
8 for organizing this important meeting and inviting  
9 us to present.  
10 My name is Kun Zhang. I am a health  
11 scientist and health services researcher with the  
12 Division of Overdose Prevention at CDC. It's a  
13 special great pleasure for me to present you an  
14 Overview of the Opioid NDC and MME Analytical File  
15 Compiled by CDC. I think my presentation is  
16 switching the gear a little bit from patient care  
17 to a more retrospective context. It's more about  
18 data and analytics.  
19 Here is my agenda. I will first give an  
20 introduction of the opioid NDC and MME analytical  
21 file, which I will just simply refer to as the  
22 analytical file hereafter, followed by the purpose

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

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

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

15 What is the analytical file? I need to  
16 switch the order of the bullets a little bit.

17 First of all, NDC stands for National Drug Code,  
18 which I'm sure most of you are familiar with. MME,  
19 as we already heard many times in the morning,  
20 stands for morphine milligram equivalent.

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

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

8 The file has been available since around  
9 2014 and has been updated annually. The major  
10 reason for the update is to add new NDCs of opioids  
11 every year.

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

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

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

7 When the opioid is a combination of opioid  
8 and other ingredient, we separate out the strength  
9 of the opioid to make the use of the file easier.

10 Oral MME conversion factors were assigned to each  
11 NDC, and we also provide documentation with  
12 detailed information on the purpose of the file,  
13 our exclusion criteria, instructions for use, and  
14 some important caveats.

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

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1 uses NDC as a unique identifier for each drug  
2 record.

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

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

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

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

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

6 Moving on to the second item on the agenda,  
7 I'm going to focus on the purpose of the analytical  
8 file and the process of developing or compiling it.  
9 As I mentioned, the file first became available  
10 around 2014. About two to three years prior to  
11 2014, when the opioid overdose epidemic started  
12 drawing more national attention, there was also a  
13 growing amount of surveillance and research on  
14 prescribing pharmaceutical opioids; for instance,  
15 studying the trends and patterns of prescribing and  
16 association between opioid misuse and overdose.

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

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

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

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

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

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

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

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

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

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

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

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

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1 data.

2 We identified opioids by using therapeutic

3 class 60, 61, 62, where 60 contains opioid agonist,

4 61 contains opioid partial agonist, and 62 only

5 contains tramadol. In this screenshot, again, you

6 can see several opioid products here, including

7 oxymorphone, oxycodone, and hydrocodone. There are

8 many therapeutic classes accounting for these over

9 300,000 NDCs, but opioids are the number one in

10 terms of its number of NDC codes.

11 Some additional steps we took, based on the

12 purpose of the file, we excluded opioids that are

13 typically used in non-outpatient settings,

14 including injectables. In other words, patients

15 don't normally get this dispensed at retail

16 pharmacies.

17 We also excluded opioids for cough and cold

18 formulations from the list. More importantly, we

19 separated out the strength of the opioid ingredient

20 when the drug is a combination of opioids and other

21 components, which is very common for opioid

22 medications, as you can see in this screenshot.

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1 Based on the opioid ingredient, we assigned

2 the type of opioid -- for instance, hydrocodone,

3 oxycodone, tramadol, fentanyl -- to each individual

4 NDC. Next, we assigned the oral MME conversion

5 factor to each NDC based on what type of opioid it

6 is. Here is an example of the conversion factors

7 we used.

8 For most opioids, it's relatively

9 straightforward to assign an MME conversion factor.

10 I only say "only" relatively for the purpose here,

11 however, for some it's much more complicated. For

12 instance, fentanyl has different forms of drugs.

13 As a result, different conversion factors need to

14 be applied.

15 In the screenshot I'm showing here -- this

16 is from RED BOOK data -- you can see fentanyl

17 transdermal patch. There's also fentanyl film, and

18 fentanyl lozenge. They have different conversion

19 factors, and it's even more complicated for the

20 fentanyl transdermal patch, which was covered by

21 Dr. McPherson and I believe Dr. Fudin as well this

22 morning.

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1 For methadone, of course -- again, you heard

2 it this morning from previous speakers -- the

3 conversion factors might depend on the dosage of

4 the methadone in milligrams. The more the

5 milligrams of methadone, the higher the conversion

6 factor. We applied the conversion factor of 3 for

7 the purpose of the analytical file, which I will

8 explain later on.

9 Here is a screenshot of the compiled NDC and

10 MME analytical file. The file basically just looks

11 like this. When users have access to the file, we

12 deliver the file itself in Microsoft Excel, as well

13 as the SAS data file. We also include the SAS

14 program so that the user can use it to link the

15 analytical file to their pharmaceutical claims data

16 or pharmacy transaction data.

17 In terms of maintaining the file, again the

18 annual update. The major reason is to add new NDCs

19 for opioids every year. It's been decreasing in

20 terms of the number of new NDCs, but it's probably

21 around 115 new NDCs every year.

22 Now that we have the file, let's talk about

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1 how to use it. Going back to the screenshot of

2 typical pharmaceutical claims data or pharmacy

3 transaction data, this is the information that is

4 normally available. The only identifier is this

5 NDC code. When you first receive the data, you

6 don't know which drugs are opioids. When you use

7 the analytical file, to join or merge the

8 analytical file with your own data, either claims

9 or pharmacy transaction data, using the NDC has the

10 key for the merge.

11 Here is a screenshot of your own data after

12 the join or merge. On the left in the blue box is

13 the information from your own data. On the right

14 in the red box is the information you merged into

15 your own data that is from the analytical file.

16 First of all, now we can tell which

17 prescription claims are opioids. As you can see,

18 only the records with information of generic drug

19 name, or strength, and conversion factor are

20 opioids. We use all this information, plus the

21 dispensed quantity, and day supply you already have

22 from your own data, and you can calculate

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1 retrospectively the prescribed daily dosage of that  
2 prescription.  
3       How to calculate the prescribed daily  
4 dosage, the goal of the analytical file is that the  
5 user can apply one formula to calculate the  
6 prescribed daily dosage with both information from  
7 the claims data or pharmacy transaction, as well as  
8 information being merged into the data, which are,  
9 of course, the dispensed quantity day supply and  
10 the strength of the opioid ingredient and the MME  
11 conversion factor.  
12       Here on the top of the slide I'm showing the  
13 formula for calculating data MME. If you compare  
14 this screenshot with the last one, the difference  
15 is there are additional columns and of the data,  
16 showing you the calculated daily dosage for that  
17 particular opioid prescription. For instance, the  
18 first one, hydrocodone, prescribed quantity of  
19 120 tablets; strength, 10 milligrams per tablet; so  
20 the calculated daily dosage is 40 MME per day.  
21       Again, it could be complicated, particularly  
22 for the fentanyl transdermal patch and methadone.

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1 Let's use the fentanyl transdermal patch as the  
2 example. The fentanyl transdermal patch and also  
3 the most prescribed fentanyl requires special  
4 consideration when calculating daily dosage because  
5 the measure of the strength is micrograms per hour.  
6       Here is a screenshot of real claims for the  
7 fentanyl transdermal patch. If you recall, when we  
8 talk about extending conversion factor to opioids,  
9 the fentanyl transdermal patch should be 0.1  
10 multiplied by 24, meaning that 0.1 micrograms of  
11 fentanyl is equivalent to 1 milligram of oral  
12 morphine. Multiplied by 24 means 24 hours in a  
13 day, so it should be 2.4.  
14       Using the 25 microgram per hour of fentanyl  
15 as an example, if we want to apply the formula  
16 directly, we need to do further adjustment, which  
17 is to take into account that one patch will be used  
18 for 3 days, which is 72 hours. So the value in the  
19 red box is the conversion factor of the fentanyl  
20 transdermal patch in this particular context. When  
21 you work with the analytical file and work with  
22 claims data, you apply the formula directly. We

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1 have this documented in detail together with the  
2 analytical file. So when we apply this value, then  
3 we would calculate the daily dosage of this  
4 25 micrograms of the fentanyl transdermal patch as  
5 60 MME per day.  
6       So again, continuing to show the fentanyl  
7 transdermal patch as an example, the screenshot  
8 here, the difference is there are two additional  
9 columns. One is showing the conversion factors we  
10 use for this analytical file, as well as the  
11 calculated daily dosage.  
12       I thought it was interesting to point out  
13 the 75 microgram per hour because it was also used  
14 as an example by Dr. McPherson and Dr. Fudin this  
15 morning. The formula here calculates the daily  
16 dosage for the 75 microgram per hour as 180, I  
17 believe which is in the range that the presentation  
18 this morning showed, but probably at the upper end.  
19       For methadone, for the purpose of using the  
20 file, we applied a conversion factor of 3 so that  
21 the formula can be applied directly. Again, this  
22 is for the purpose of research, surveillance, or

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1 monitoring population drug utilization of opioids.  
2 It's not a sliding conversion factor here, however,  
3 we also want to show you some real methadone  
4 prescription data we just obtained from IQVIA, the  
5 National Level Dispense Data of 2019.  
6       Methadone prescriptions account for about  
7 1 percent of total opioid prescription, excluding  
8 buprenorphine for MOUD in 2019. So 1 percent,  
9 that's about 1.45 million prescriptions in 2019.  
10 Interestingly, when you look at the distribution of  
11 strength per unit among all the methadone  
12 prescriptions, the 5-milligram tablet accounts for  
13 about 24 percent, and the 10-milligram methadone  
14 accounts for about 76 percent.  
15       So they basically account for all of the  
16 prescribed methadone prescriptions in 2019, which  
17 means if you look at the daily dosage and  
18 micrograms for methadone among all the  
19 prescriptions, the daily dosage would be an  
20 incremental of either 5 milligrams or  
21 10 milligrams. We think this is important for  
22 calculating the conversion factors for methadone in

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1 a clinical setting and also helpful for the  
2 discussion, in general, around the conversion  
3 factors for methadone.  
4 We are also providing the distribution of  
5 daily micrograms of methadone prescriptions in  
6 2019. As you can see, the mean daily and microgram  
7 methadone prescription is about 36, and you see all  
8 these percentiles. The median is 30 milligram.  
9 Next, I'll just go over the next few slides  
10 very quickly. These are some real applications of  
11 the file. The first thing is for surveillance  
12 purposes, we use the file, then link with pharmacy  
13 transaction data to calculate average data MME per  
14 prescription, of course, retrospectively, from 2006  
15 to 2015. We calculated county-level prescribed MME  
16 per capita for 2015.  
17 Just as an example also, using the  
18 analytical file for surveillance purposes, this is  
19 another example. This is a web application at CMS.  
20 CMS has these tools for users to track state-level  
21 prescribing of opioids, as well as the average  
22 daily dosage of the MME per prescription amount,

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1 either the Medicaid population or the Medicare  
2 population.  
3 This is another example of the state PDMP  
4 program using the analytical file with their PDMP  
5 data to create statistics on their PDMP data  
6 dashboard. This particular one is from, I believe,  
7 Rhode Island, where they show the number of  
8 prescription -- can you still hear me?  
9 DR. CHAI: Yes, I can hear you.  
10 DR. ZHANG: My Adobe is showing connection  
11 lost.  
12 DR. CHAI: Gideon, or if --  
13 DR. ZHANG: It's back. Sorry about that.  
14 DR. CHAI: I can see your slide. It's back?  
15 Okay. Thank you.  
16 DR. ZHANG: Okay. Great. Thank you for  
17 confirming.  
18 This is showing the number of prescriptions  
19 over what they found as high-dose opioids. I  
20 believe it's over 90 per day. Again, this is  
21 retrospectively calculating the prescribed 80 doses  
22 for opioid prescriptions in Rhode Island, and it

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1 shows the next figure longitudinally from 2017 to  
2 2020.  
3 I believe you can hear me, but I'm still  
4 showing that message. I'll just keep moving.  
5 The next slide, I'm trying to show some  
6 examples of published studies, mainly research,  
7 using the analytical file together with pharmacy  
8 claims or pharmacy transaction data for all these  
9 research topics.  
10 This is only a very, very small portion of  
11 published studies using the analytical file. There  
12 are tons of more studies out there looking at  
13 prescribing patterns, as well as, most commonly,  
14 associations between prescribing or use and  
15 overdose, as well as other adverse health outcomes.  
16 Lastly, I want to go over some important  
17 distinctions between the analytical file and the  
18 table of MME conversion factors we published with  
19 the CDC prescribing guideline. Again, the  
20 analytical file is not intended for any clinical  
21 decision making by clinicians, particularly primary  
22 care clinicians, when prescribing opioids.

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1 The conversion factors we included in the  
2 analytical file should not be used directly by  
3 clinicians to calculate daily dosage for patients.  
4 I think the methadone is a great example, as well  
5 as the fentanyl transdermal patch. The MME  
6 conversion factors in this file do not constitute  
7 any clinical guidance or recommendations for  
8 converting patients from one form of opioid  
9 analgesics to another.  
10 For clinical decision making, in March 2016,  
11 CDC released the guideline for prescribing opioids  
12 for chronic pain. We also developed and published  
13 the guideline to provide recommendations for  
14 prescribing opioid pain medication for patients 18  
15 and older in primary care settings.  
16 The recommendations focused on the use of  
17 opioids in treating chronic pain in all patient  
18 settings, so the guideline is not intended for  
19 patients who are in active cancer treatment, or  
20 palliative care, or end-of-life care, which we  
21 covered a lot this morning as well.  
22 The CDC guideline addresses patient-centered

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

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

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

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

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

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

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

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

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

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

21 DR. ZHANG: Thank you.

22 DR. CHAI: Yes, thank you.

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1 Next, we will be hearing from  
 2 Dr. Pittaway-Hay, followed by Dr. Molinari, calling  
 3 in from a very late hour from the United Kingdom.

4 We're very thankful to have you here to provide  
 5 insight into the medicines and healthcare products'  
 6 regulatory agencies' perspective on MMEs.

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

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

10 DR. PITTAWAY-HAY: Wonderful. Thank you.

11 Presentation – Justin Pittaway-Hay

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

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



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

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

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

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1 This is a little bit akin to a U.S. panel.  
2 The Opioid Expert Working Group most  
3 recently reconvened in early 2019 in light of the  
4 growing concerns about opioids, the overuse and  
5 misuse of opioids, and particularly in non-cancer  
6 indications. This was leading to a growing problem  
7 of dependence and addiction which was seen in the  
8 UK, which is, of course, seen in other  
9 jurisdictions equally.

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

16 The members of the expert working group in  
17 the UK are made up of various experts in various  
18 scientific disciplines across some pain management,  
19 nursing; pharmacy; anaesthesia; old-age medicine,  
20 as well as medicine in children; and a lay member  
21 as well; and also, of course, a pharmacologist.  
22 I would just like to highlight that I am not

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

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

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

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

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

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

22 We looked at opioid conversion tables of

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

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

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

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

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

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

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

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

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

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

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

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

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1 not, but there was a lot of information missing  
2 from the tables. Whether that may have been due to  
3 non-prescribing in that jurisdiction or in that  
4 country, or for other reasons, it wasn't looked  
5 into any further.  
6 I'll be very quick on this slide. This is  
7 about dose reduction because the purpose of our  
8 talk was more to identify a maximum or a total  
9 daily dose, and this has also been discussed in  
10 earlier talks as well. But most of them included  
11 some sort of warning of how to do a dose reduction;  
12 that there needed to be a dose reduction in most  
13 cases, and especially when giving at high doses.  
14 As I said, most of these tables we  
15 identified, they were accompanied with notes for  
16 consideration. Some of the examples we've  
17 discussed in earlier talks as well that there was  
18 caution needed when using it for opioid switching.  
19 We needed to consider the variability in  
20 pharmacokinetics, so that's how the body handles  
21 the medicine, and pharmacodynamics, that's how the  
22 medicine affects the body both within and between

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1 patients.  
2 Modified-release formulations needed to be  
3 accounted for, and data may have been derived from  
4 pooled data, and of course residual drug in the  
5 patient's systems must be accounted for. So these  
6 were some of the examples that were associated with  
7 the tables that we identified.  
8 Again, this was highlighted by Professor  
9 McPherson's talk as well, this directional  
10 inequality. But many of the reviews or tables  
11 actually noted that opioid conversion tables may be  
12 overly simplified and that clinicians need to be  
13 aware that there is that directional difference in  
14 opioid equivalents, and that just can't be  
15 reversible in any direction.  
16 Many opioid conversion tables included some  
17 indication of a limitation to their own table.  
18 They said there was failure to standardize to  
19 reference opioids. There is also an inclusion of a  
20 wide range of doses, and they are sometimes  
21 determined by single doses or acute pain, which of  
22 course makes them inapplicable for multiple

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1 administration settings. It's also been  
2 highlighted that sometimes computations have been  
3 used instead of clinical trial data.  
4 Published opioid equivalence tables of  
5 course provide a clinically useful tool for  
6 clinicians, but they have been known to be beset  
7 with limitations. We know that there are  
8 limitations in them, and they are known, in regard  
9 to the underlying data, to have issues of  
10 directionality and ease of use. Of course, a  
11 patient may be on many different opioids, and  
12 adding them all up for a busy clinician may be  
13 difficult. This is why we see more and more  
14 calculators and online calculators, and now I guess  
15 with apps as well.  
16 There is also wide variability in conversion  
17 factors between tables and studies that need to be  
18 identified. Subsequently, this has therefore an  
19 impact on recommending a total maximum and total  
20 daily pure dose, which my colleague, Dr. Molinari,  
21 will talk in a little bit more detail in the next  
22 talk. Thank you very much.

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1 DR. CHAI: Thank you, Dr. Pittaway-Hay.  
2 If we can just transition to Dr. Molinari.  
3 Thank you, Dr. Molinari.  
4 DR. MOLINARI: Thank you. I hope you all  
5 can hear me clearly. Can you hear me?  
6 DR. CHAI: Yes, I can hear you.  
7 Presentation – Maria Molinari  
8 DR. MOLINARI: Good afternoon, everybody.  
9 Thank you to the FDA for inviting us to this  
10 workshop and to be able to hear from all the  
11 experts in the field of pain. Justin looked at the  
12 conversion tables, and my job was to look at the  
13 potential maximum daily dose of morphine  
14 equivalents and how we can improve the information  
15 for prescribers.  
16 The question on the need of a maximum  
17 morphine equivalent dose per day was first  
18 discussed in an opioid expert working group meeting  
19 in June 2019. It was noticed that a number of  
20 guidelines on the management of chronic non-cancer  
21 pain provided inconsistent information with the  
22 maximum morphine equivalent daily dose beyond which

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1 the risk of serious adverse reaction, including  
2 dependence, exceeded the benefit of pain relief.  
3 The expert working group considered that  
4 further research was required to provide evidence  
5 in support of a preferred maximum daily dose for  
6 which benefit to risk may be favorable and also on  
7 the calculation of morphine equivalents.  
8 Justin and I were asked to prepare a paper  
9 that could provide an overview of the current  
10 situation on opioid equivalent tables and maximum  
11 daily dose recommendation for non-cancer pain. The  
12 review looked at different guidelines for chronic  
13 non-cancer pain in the UK and worldwide. And as I  
14 said before, these guidelines provide inconsistent  
15 information on the maximum equivalent dose of  
16 morphine.  
17 For example, with the first two updates to  
18 the guidance, the U.S. Department of Health in 2016  
19 suggested to reconsider the individual benefits and  
20 risks when increasing the dosage above  
21 50 milligrams of morphine equivalents a day and  
22 avoid increasing dosage more than 90 milligrams per

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1 day, or carefully justify the decision to titrate  
2 dosage to 90 milligrams a day.  
3 In 2017, the Canadian Practice guideline  
4 also restricted the prescribed dose to less than  
5 90 milligrams morphine equivalents a day. The  
6 Australian and New Zealand guideline provides  
7 100 milligrams of morphine equivalents a day limit  
8 above which specialist advice should be sought.  
9 In the UK, more recently, the Scottish  
10 Intercollegiate Guidelines Network was updated in  
11 August 2019 and is now recommending a new high  
12 limit of 90 milligrams, or even 50 milligrams,  
13 which is in line with the CDC.  
14 This is a table, and we put a table together  
15 to try to understand what were the differences in  
16 guideline. There was obviously not just the lack  
17 of unanimity of what is the safest maximum morphine  
18 equivalent daily dose, but also there are a number  
19 of conversion charts and opioid calculators  
20 available that have shown significant difference  
21 now to determine opioid conversion to morphine  
22 equivalent doses.

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1 What was the outcome of the Expert Working  
2 Group? The EWG thought that a ready available  
3 conversion table was necessary. Ideally, a  
4 conversion table for every individual opioid would  
5 be helpful and facilitate prescribers. They also  
6 recommended it would be useful to establish a  
7 maximum range for pediatric dosing, although it was  
8 recognized there were currently no guidelines for  
9 treating children with opioids, and the posology  
10 calculates the milligram per kilogram at the  
11 moment.  
12 We sought the CHM opinion on a proposed  
13 maximum daily dose on morphine and equivalents, and  
14 tried to find what was the best conversion table  
15 available and what was the best way to inform  
16 prescribers. We presented many of the papers that  
17 were used in the different guidelines to discuss  
18 our proposal with CHM. Although there were some  
19 differences, they all agreed that it is a  
20 substantial risk associated with doses above  
21 90 milligrams per day.  
22 Also, our colleagues from the pediatric

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1 [indiscernible], they reviewed the pediatric  
2 literature on opioids for the treatment of chronic  
3 non-cancer pain. They discussed the lack of  
4 evidence for treatment in pediatric chronic and  
5 non-cancer pain. Literature reports identified  
6 inadvertent poisoning, risk of addiction in  
7 adolescents, and no really recommendation for  
8 maximum equivalent of morphine dose in patients  
9 below the age of 18.  
10 Mainly, they used other conversion factors  
11 that often are used critically in children, and  
12 there is much less evidence for morphine equivalent  
13 dose than for adults, and there are very few  
14 studies of opioid equivalents and conversion in the  
15 pediatric population. Opioid dosing in the  
16 pediatric population tends to be weight based,  
17 although flatter [indiscernible] dose is based on  
18 age [indiscernible], opioid posology in pediatric  
19 obesity, for example, is not well understood.  
20 The Pediatric Expert Working Group concluded  
21 that it was inappropriate to extrapolate any adult  
22 morphine equivalent daily dosing recommendation to

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

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

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

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

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

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

18 Clarifying Questions to Speakers

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

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

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

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

22 As a gentle reminder, this is the clarifying

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1 questions for panelists or presenters session, so  
2 please keep all questions and answers to clarifying  
3 questions. We do have panel discussions scheduled  
4 for tomorrow, so at this time we'll have clarifying  
5 questions. And to note the time, we will be ending  
6 at 2:50 in order to have a break for 10 minutes  
7 before our public comment session to start at  
8 3 p.m. So we can go until 2:50.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 those public comment session speakers if they can  
2 stay on to work with the AV team to be able to make  
3 sure that your audio is connected.  
4 For all others, we thank you for your time.  
5 For presenters, please don't be alarmed. We're  
6 going to have to clear the room, the presenter room  
7 a bit, in order to allow for the public comment  
8 session speakers to be brought into the presenter  
9 room. I'm talking virtual rooms obviously; but if  
10 you could continue to stay on the meeting to hear  
11 the very important public comment session speakers'  
12 comments, but you will be moved down to the  
13 participant room.  
14 So thank you for your time, and we'll see  
15 you in 10 minutes at 3 o'clock; or more than  
16 10 minutes, but 3 o'clock.  
17 (Whereupon, at 2:48 p.m., a recess was  
18 taken.)  
19 DR. CHAI: Hello, everyone. Welcome back  
20 from the break, and thank you for your patience as  
21 we work to ensure that all the connections are  
22 running smoothly.



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1 At this time, I'll now turn over moderation  
2 to Dr. Tamra Meyer, who will be walking us through  
3 the public comment session.  
4 Thank you, Dr. Meyer.  
5 Public Comment Session – Tamra Meyer  
6 DR. MEYER: Thank you, Dr. Chai.  
7 Welcome back again, everyone. We're ready  
8 to get started. We're about to begin the public  
9 comment session. As Dr. Chai mentioned, my name is  
10 Tamra Meyer. I'm an epidemiologist and a team lead  
11 in the Office of Surveillance and Epidemiology in  
12 CDER, and I'll be moderating this session.  
13 There were more initial requests to speak  
14 during this session than we could accommodate, so  
15 FDA lengthened the public comment session to allow  
16 as many people as possible to speak, and we  
17 conducted a lottery, a lottery to randomly select  
18 35 speakers to present today.  
19 Since this is a virtual meeting,  
20 confirmation to speak and prior audio testing was  
21 necessary to ensure that the speakers could be  
22 heard during the live virtual meeting, and you

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1 heard today that that can sometimes go awry as  
2 well. Unfortunately, we did not receive  
3 confirmation from all the selected speakers, and  
4 some of the confirmed speakers let us know today  
5 that they weren't able to join.  
6 So you will hear me note this as I moderate  
7 the session. We encourage those who were selected  
8 and unable to confirm their participation, those  
9 who were not selected to present today, and anyone  
10 with comments or materials to share with us to  
11 submit them to the docket, so that they can be part  
12 of the public record for this meeting.  
13 Both the FDA and the public believe in a  
14 transparent process for information gathering, and  
15 to ensure the transparency at this public comment  
16 session, FDA believes it is important to understand  
17 the context of an individual's presentation.  
18 For this reason, FDA encourages you, the  
19 public comment session speaker, at the beginning of  
20 your oral statement to state any financial or other  
21 relationships that you may have related to this  
22 meeting topic or to your presentation. If you

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1 choose not to provide this context at the beginning  
2 of your statement, it will not preclude you from  
3 speaking today.  
4 The FDA and this panel place great  
5 importance on the public comment session process,  
6 and the insights and the comments that you provide  
7 can help the agency and this panel in their  
8 consideration of the issues before them today.  
9 That said, in many instances and for many  
10 topics, there will be a variety of opinions. One  
11 of our goals for today is for this public comment  
12 session to be conducted in a fair and open way,  
13 where every participant is listened to carefully  
14 and treated with dignity, courtesy, and respect.  
15 Therefore, please speak only when recognized by me,  
16 the moderator. Thanks for your cooperation.  
17 Since this is a virtual meeting, I want to  
18 review the process for this session. I will call  
19 your speaker number when it is time for your  
20 presentation. If you provided slides, one of our  
21 staff will open the slides for you. You may  
22 advance your own slides, but you can also ask for

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1 us to advance them for you.  
2 You will see the countdown timer on the  
3 screen, and we will start this timer once you start  
4 your presentation. When your time is up, I will  
5 break in to ask you to wrap up your comments  
6 promptly. If you have additional comments that you  
7 are unable to provide, you can submit them to the  
8 docket so that they become part of the public  
9 record, and FDA can consider them with the rest of  
10 the meeting materials and discussion that we hear  
11 today.  
12 Okay. I think we're ready to move to  
13 speaker number 1.  
14 Speaker number 1, your audio should be  
15 connected now. Will you please begin and introduce  
16 yourself?  
17 DR. SAN BARTOLOME: Thank you.  
18 Good afternoon. My name is Mario San  
19 Bartolome. I am the vice chair of the American  
20 Society of Addiction Medicine, Practice Management,  
21 and Regulatory Affairs Committee. I'm an addiction  
22 medicine specialist and a board-certified physician

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1 in both addiction medicine and family medicine. I  
2 have no conflicts to disclose.  
3 Thank you for the opportunity to offer  
4 comment on behalf of the American Society of  
5 Addiction Medicine. The use of morphine milligram  
6 equivalents, or MME, as a metric to gauge overdose  
7 risk can be problematic in the field of addiction  
8 medicine because the MME thresholds that indicate  
9 higher risk for opioid analgesic used to treat pain  
10 do not translate well to opioids used to treat  
11 opioid-use disorder, or OUD, and in particular,  
12 methadone and buprenorphine.  
13 The CDC guideline for prescribing opioids  
14 for chronic pain note that most experts generally  
15 agreed that increasing doses 50 or more MME per day  
16 increase overdose risk without necessarily adding  
17 benefit for pain control or function. Key to this  
18 recommendation is the underlying premise that  
19 opioids are being used to treat chronic pain, and  
20 accordingly, benefits were assessed in terms of  
21 pain control and function, and harms were evaluated  
22 in terms of overdose risk.

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1 Importantly, the benefits and risks of using  
2 opioids to treat OUD, either methadone or  
3 buprenorphine, should be evaluated differently.  
4 Both medications have been demonstrated to decrease  
5 overdose risk when used to treat OUD, and both have  
6 been demonstrated to improve health and social  
7 outcomes.  
8 Equally as important, recommended dosages of  
9 methadone and buprenorphine, when used to treat  
10 OUD, differ from recommended doses for pain  
11 treatment. A usual daily dose of methadone ranges  
12 from 60 to 120 milligrams, and evidence suggests  
13 that 16 milligrams per day or more of buprenorphine  
14 may be more effective than lower doses.  
15 Converting these recommended dosages to MME  
16 reveal that they exceed the CDC recommendations  
17 regarding MME for chronic pain. The thresholds  
18 conflict with methadone and buprenorphine  
19 clinically recommended and FDA-approved dosages.  
20 Applying MME thresholds designed to minimize  
21 overdose-related harm caused by opioids prescribed  
22 for chronic pain to opioids used for addiction

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1 treatment would have a perverse effect on limiting  
2 addiction treatment effectiveness, and potentially  
3 increasing opioid overdose deaths.  
4 This nuance may be confusing among  
5 policymakers and payers attempting to set policies  
6 to prevent opioid overdose by limiting MME, as well  
7 as among state medical board officials attempting  
8 to enforce clinical guidelines and encourage use of  
9 opioid analgesics.  
10 As such, ASAM strongly urges FDA and other  
11 authorities to exclude methadone and buprenorphine  
12 used to treat OUD from any policies intended to  
13 reduce opioid overdose-related mortality by  
14 limiting MME. Higher MME of these medications are  
15 necessary and clinically indicated for the  
16 effective treatment of OUD. Thank you very much  
17 for your time.  
18 DR. MEYER: Thank you very much, speaker  
19 number 1.  
20 Speaker number 2 did not confirm their  
21 participation for today, so we will now move to  
22 speaker number 3.

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1 Speaker number 3, your audio should be  
2 connected. Please begin and introduce yourself.  
3 Please state your name and any organization you are  
4 representing for the record.  
5 MR. AUBRY: Could they put up my slides  
6 also?  
7 Good afternoon. My name is Larry Aubry. I  
8 would like to thank the FDA for this opportunity.  
9 I have no conflicts to disclose.  
10 Opioid doses above 90 MME per day are  
11 labeled as high risk due to the disproportion and  
12 association -- in other words, direct  
13 correlation -- with addiction abuse and overdose  
14 deaths. We have cut prescriptions above 90 MME by  
15 over 70 percent over the last decade.  
16 As you see the linear regression model for  
17 treatment admissions as a function of prescriptions  
18 above 90 MME, you would expect a positive direct  
19 correlation if we're basing policy on reducing  
20 prescription opioids as a means to cut treatment  
21 admissions and overdose deaths. Instead, we have a  
22 correlation in excess of negative 90 and understand

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1 that a value of negative 1 is a perfect inverse  
2 correlation.  
3 Next, we do a model of comparing a  
4 prescription opioid death as a function of  
5 prescriptions above 90 MME, and though the model is  
6 not as, let's say, clean as the other models, the  
7 key is that, again, it's not a positive direct  
8 correlation; it's negative. It's inverse.  
9 The next slide is any opioid overdose death,  
10 meaning illegal drugs, too, because many people  
11 will say, hey, taking prescription opioids leads  
12 right to overdose deaths from heroin and other  
13 illegal drugs; again, negative correlation. The  
14 next one is total overdose deaths, and again,  
15 significantly negative correlation, and in fact our  
16 overdose deaths are now above 90,000 for this year.  
17 In conclusion, I'd like to say that,  
18 basically, even when you look at simple linear  
19 regression, it illustrates the fact that the  
20 patterns are inverse and, basically, it's not just  
21 science; it's common sense. There's no direct  
22 positive correlation. We need to stop measuring

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1 success in tapering and discontinuation and stop  
2 the subordination of patients rights.  
3 Basically, 18 million Americans are being  
4 subjected to this force and coerced tapering  
5 without consent. Patients need this medication for  
6 functionality, and their families also need it so  
7 that we can function as a group. There's no logic.  
8 The data shows an inverse correlation. It's not a  
9 positive direct correlation. Thank you.  
10 DR. MEYER: Thank you very much, speaker  
11 number 3.  
12 Our next speaker is speaker number 4  
13 Speaker number 4, your audio should be  
14 connected now. Will you begin and introduce  
15 yourself? And please state your name and any  
16 organization you are representing for the record.  
17 MS. OGDEN: Please put my slides up. Thank  
18 you.  
19 Good afternoon. My name is Kristen Ogden,  
20 and I am co-founder of Families for Intractable  
21 Pain Relief. I have no financial issues to  
22 disclose. I speak today on behalf of a very small

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1 subset of chronic pain patients who suffer from  
2 severe constant, incurable pain with cardiovascular  
3 and endocrine complications. When undertreated,  
4 such pain has devastating effects on cardiovascular  
5 and endocrine systems, and can lead to premature  
6 death.  
7 From the perspective of these patients and  
8 their families, MME-based policies have not worked.  
9 There are many variables, and patient response  
10 varies widely. MME thresholds established in  
11 policies have most often been used to set dose  
12 ceilings and reduction targets. The result has  
13 been an increase in patient harm, not improvement  
14 in patient care.  
15 MME policies have caused incalculable harm  
16 to patients, families, physicians, and pharmacists.  
17 They have harmed our country, our citizens who  
18 suffer from the constant reinforcement of the  
19 opioids are a bad stigma that fosters loss of  
20 empathy for fellow human beings and irrational fear  
21 of opioid drugs and the people who use them.  
22 High doses are indeed needed by some

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1 intractable pain patients as a last-resort  
2 treatment when all else has failed. These patients  
3 often suffer from extremely painful, incurable  
4 diseases that involve neuroinflammation, such as  
5 arachnoiditis and connective tissue disorders, such  
6 as Ehlers-Danlos syndrome.  
7 Efficacious doses for some of these patients  
8 are in the 2000 to 3000 MME range. If success is  
9 achieved with a high-dose opioid treatment regimen,  
10 if goals are met for pain control, functional  
11 capability, and quality of life, patients should  
12 not be tapered off medications that work for them.  
13 The bottom line here, MME should not be used  
14 as a threshold for prescribing or dispensing  
15 medications or for targeting and disciplining  
16 doctors. We need to restore physician discretion  
17 to diagnose and prescribe. Failure to do so will  
18 allow the continuation of preventable harm. In  
19 effect, this amounts to torture of intractable pain  
20 patients.  
21 This man is my husband, Louis Ogden, who has  
22 suffered pain since the age of 6. After decades of

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1 attempting treatment with many modalities, many  
2 medications, and many therapies, he started  
3 high-dose opioid therapy in 2010 at the age of 60.  
4 From 2010 to 2018, he had excellent pain relief  
5 with no dose escalations and his best quality of  
6 life as an adult.  
7 Then his pain medication dose was reduced  
8 because 2900 MME was too high. He no longer has  
9 excellent pain relief, improved function, and good  
10 quality of life. He should not have to suffer  
11 because of an arbitrary number, the MME, is too  
12 high. Freedom from pain to the extent achievable  
13 is the most fundamental of all human rights. Thank  
14 you for the opportunity to comment.  
15 DR. MEYER: Thank you very much, speaker  
16 number 4.  
17 Is speaker number 5 still connected? Can  
18 you hear us?  
19 (No response.)  
20 DR. MEYER: Okay. I think we're having some  
21 technical difficulties with speaker number 5.  
22 We'll come back to them at the end.

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1 Speakers number 6 through 8 unfortunately  
2 could not confirm their participation for today, so  
3 our next speaker is speaker number 9.  
4 Speaker number 9, your audio should be  
5 connected now. Will you begin and introduce  
6 yourself? And please remember to state your name  
7 and any organization you are representing for the  
8 record.  
9 MS. BUCK: Hi. My name is Shirley Buck.  
10 I'm representing American Pain and Disability  
11 Foundation. I have no financial associations to  
12 disclose. I'd like to say thank you very much for  
13 the opportunity to speak with everyone at the FDA.  
14 I'd like to let you know that the  
15 90 morphine milligram equivalency was created out  
16 of the blue. There is no scientific proof about  
17 it; none. There is no testing, no nothing, it's  
18 just out of the wind created.  
19 This is not fair to chronic pain patients.  
20 Many, as the last speaker said, are on much, much  
21 higher doses. They've lost their entire lives,  
22 their homes, their jobs, their families, and

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1 everything. That is not how you treat a human  
2 being, especially when they're ill or have been  
3 injured permanently.  
4 Here's a good example. Imagine if everyone  
5 was directed -- and this includes everyone at the  
6 FDA and all chronic pain patients -- to only be  
7 allowed to wear a size 4 pants. Even if it didn't  
8 fit, you still had to wear them. It doesn't work.  
9 Do you understand what I'm saying? I hope you do.  
10 Hopefully, I'll leave that with you to think about.  
11 The cost effectiveness with pushing everyone  
12 on to buprenorphine and Suboxone, even for chronic  
13 pain patients, they're putting chronic pain  
14 patients on Suboxone. The drugs are astronomically  
15 high when you compare it to the usual opioid  
16 medication.  
17 I lost my place; I'm sorry.  
18 Illicit drug overdoses are up 1400 percent,  
19 not prescription opiates. That is about as low as  
20 you can get, besides zero. The chronic pain  
21 patients haven't done anything wrong, but yet their  
22 lives have been completely put in turmoil. Many

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1 have committed suicide just like our veterans.  
2 They're going through the same thing. Most of them  
3 have been completely cut off. These are our  
4 veterans. What is wrong with America? Geez! Some  
5 of them are quadruple amputees. They can't get  
6 pain medicine. It's inexcusable; it's inhumane  
7 torture.  
8 I would seriously like to ask for everyone  
9 at the FDA to highly consider getting rid of the  
10 90 MME limit. It's just not feasible for most  
11 patients in chronic pain, and it isn't a way to  
12 treat pain for anyone. I wouldn't wish this on  
13 anyone. Thank you for the opportunity to speak.  
14 DR. MEYER: Thank you very much, speaker  
15 number 9.  
16 I believe we have speaker number 5  
17 connected. Can you confirm that you can hear us  
18 and we can hear you?  
19 (No response.)  
20 DR. MEYER: Speaker number 5, can you say  
21 something?  
22 (No response.)

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1 DR. MEYER: Okay. I think we're still  
2 having some technical difficulties with  
3 speaker 5 --  
4 MS. DIFILIPPANTONIO: I'm here.  
5 DR. MEYER: Oh. Can you say that again?  
6 MS. DIFILIPPANTONIO: I'm here.  
7 DR. MEYER: Okay. Hi. Your audio is  
8 connected. We can hear you. Will you go ahead and  
9 begin and introduce yourself? Please remember to  
10 state your name and any organization you are  
11 representing for the record.  
12 MS. DIFILIPPANTONIO: Speaker number 5 is  
13 here.  
14 (Pause.)  
15 AV TECH: Carrie, you can go ahead.  
16 MS. DIFILIPPANTONIO: Can anyone hear me?  
17 AV TECH: Yes, ma'am. We can hear you. Can  
18 you hear us?  
19 (No response.)  
20 DR. MEYER: Okay. This is Tamra Meyer.  
21 Let's go ahead and move on to the next speaker, and  
22 see if we can get Speaker 5's audio fixed, and

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1 we'll come back to them  
2 Alright. That makes our next speaker,  
3 speaker number 10.  
4 Speaker number 10, your audio should be  
5 connected. Please introduce yourself. State your  
6 name and any organization you're representing for  
7 the record.  
8 DR. DeGEORGE: Sure. Thank you. Can I have  
9 my slides, please?  
10 My name is Mike DeGeorge, and I'm the vice  
11 president of medical affairs of Collegium  
12 Pharmaceuticals, a company committed to being the  
13 leader in responsible pain management. We felt  
14 compelled to comment because we believe the  
15 misapplication of MMEs is negatively impacting both  
16 patient care and public health, particularly when  
17 it comes to atypical opioids, and among those  
18 tapentadol, which is a product in Collegium's  
19 portfolio.  
20 As we heard from this morning's speakers,  
21 the benefits and risks of atypical opioids are not  
22 solely dependent on activity at the mu receptor,

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1 and as such, MMEs may not provide an adequate  
2 measure of dose equivalency.  
3 In addition, atypical opioids have  
4 FDA-approved dose limits in their label specific to  
5 active ingredients and informed by safety findings.  
6 This difference is only partially reflected in the  
7 published CDC guideline, as they do not include  
8 conversion factors for tramadol or buprenorphine.  
9 However, this is not the case with tapentadol.  
10 Taking the CDC conversion factor of 0.4 for  
11 tapentadol, as well as the 90 MME recommended  
12 dosage limit, the maximum daily dose of tapentadol  
13 would be 225 milligrams per day. This is  
14 significantly less than the average therapeutic  
15 dose of approximately 3[00]-400 milligrams per day  
16 identified by phase 3 studies and less than half of  
17 the FDA-approved maximum daily dose.  
18 This impacts patient care, as clinicians  
19 report a reluctance to prescribe tapentadol based  
20 on fear of the optics of having their doses exceed  
21 MME limits and concern that they won't be able to  
22 prescribe an efficacious dose for their patients.

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1 This is problematic beyond the impact of patients,  
2 as it also has the potential to negatively impact  
3 public health.  
4 Four recent real-world evidence studies have  
5 shown that tapentadol has the lowest rate of  
6 serious adverse events and no reported deaths in  
7 one study. The extended-release version of  
8 tapentadol had lower rates of abuse than ADFs and  
9 non-ADF ER comparators.  
10 Abuse of tapentadol was infrequent relative  
11 to other opioids among individuals entering  
12 treatment for opioid-use disorder, and even when  
13 comparing to other atypical opioids, tapentadol, a  
14 Schedule II product, had lower rates of abuse than  
15 buprenorphine, a Schedule III product, on a  
16 population basis, and similar abuse when adjusted  
17 for utilization. Any artificial barrier to  
18 tapentadol prescribing may lead clinicians to drugs  
19 that have not performed as well with regard to  
20 misuse, abuse, diversion, or overdose over the past  
21 decade.  
22 In conclusion, we applaud FDA efforts to

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1 examine the science behind MME and their  
2 application. We've seen the problems with MME are  
3 amplified when applied to atypical opioids, and  
4 particularly tapentadol. Real-world evidence  
5 related to tapentadol has demonstrated relatively  
6 lower rates of abuse, misuse, diversion, and death,  
7 and its utilization may be, in part, reduced by an  
8 artificially low MME limit, which has the potential  
9 to negatively impact public health.

10 Because of this, we believe tapentadol  
11 should be treated like other atypical opioids and  
12 should not have a specific MME conversion, and  
13 instead prescribers should be allowed to dose the  
14 medication as per the FDA approved label. Thank  
15 you for your time.

16 DR. MEYER: Thanks very much, speaker  
17 number 10.

18 Okay. Let's try speaker number 5 again.

19 Carrie, can you hear us; and say something?  
20 (No response.)

21 DR. MEYER: It looks like we might have lost  
22 her again, so we will try speaker number 14.

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1 MS. DIFILIPPANTONIO: I'm --  
2 DR. MEYER: I'm sorry.  
3 Carrie, are you there?  
4 MS. DIFILIPPANTONIO: I am here.  
5 DR. MEYER: Perfect, and we can hear you  
6 well.

7 Okay. Go ahead and introduce yourself.  
8 State your name and any organization you are  
9 representing for the record.

10 MS. DIFILIPPANTONIO: My name is Carrie  
11 Difilippantonio. I'm a mom, a daughter, and a  
12 granddaughter of rare diseases; seem to collect  
13 them.

14 My first encounter with regulating opioids  
15 was after a Ganz procedure, which is where they  
16 break your pelvis in three places and put screws  
17 and cadaver parts in. I was sent home with a  
18 script for pain medication, and insurance said,  
19 "No. Prescribe this instead." Then after mailing  
20 the script, I turned it in, and they rejected that  
21 again. For 32 days, I was passive suicide or  
22 making plans, and I would just ask for help, can

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1 you take me off that. My son has three of my rare  
2 diseases, and I advocate for him so that he doesn't  
3 have to.

4 Patients living in the agony hear the words,  
5 "opioid epidemic" or "opioid crisis." We get  
6 triggered. We have medical PTSD due to medical  
7 abandonment, harassment, profiling by pharmacies,  
8 laws, doctors, and we are extremely questioned  
9 about why we need meds. This means we have to  
10 prove to the doctor that we are sick or have this  
11 condition, and that's not what it's supposed to do.

12 I recommend that everybody look at United  
13 States House of Representatives number 747,  
14 released in December of 2019. It talks about the  
15 War on Drugs and how we've gotten nowhere, and that  
16 it's just hurting people that are dependent. I'm  
17 bed-bound because I don't get pain meds at work.

18 I just wanted to point out that resolution.  
19 And it's 25 things, I think, it says about what  
20 government has done and how it hurt us; for  
21 example, like Nixon's War on Drugs because him and  
22 his sidekick didn't like blacks or any other

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1 ethnicities.

2 At the end of their resolution, they say,  
3 "Whereas after almost 50 years, the War on Drugs  
4 has yet to achieve its goals, and whereas there has  
5 been no formal action by the United States  
6 government, abuse and to treat the war on drugs is  
7 a health issue. Now, therefore it be resolved in  
8 the sense of the House of Representatives."  
9 They're not going to pass any more law around  
10 opioids.

11 Another thing that is a big problem is  
12 pharmacies. Some of them, I don't know, they just  
13 have a God sense. They hold meds ransom. I am a  
14 stage 4 breast cancer survivor -- or not survivor  
15 but sponsor. Her pharmacist would not hand over  
16 the drugs.

17 Chronic pain is an exemption, and it's been  
18 overlooked. We are dependent on it, and one of the  
19 [indiscernible] did not want to make statistics,  
20 but only six, and this was a peer-reviewed  
21 scientific journal that says only 6 percent of  
22 patients become addicted. That's very, very

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1 important to understand.  
2 Forced tapering and patient abandonment, I  
3 was cut off cold turkey from my pain doctor. Then  
4 about a week later, my son called 911, and he saved  
5 my life because I had 3 to 5 minutes left of life.  
6 And while I was waiting for my COVID test to be  
7 admitted, I had a series of mini heart attacks, and  
8 then a couple weeks after that, a series of  
9 strokes. I have lost memory for at least 9 months.  
10 I really hope that the pendulum swings back  
11 to the middle because you're really hurting moms,  
12 dads, grandpas. My grandma died last fall, and  
13 they took away her pain medication and kicked  
14 everybody out of the room.  
15 I do have an advocacy group, Pain Awareness  
16 Warriors, and we call each other's hospitals to  
17 make sure that we're getting the medication that we  
18 need. And if they're not --  
19 DR. MEYER: Speaker number 5, I'm so sorry.  
20 Your time is up. Can you just please wrap up your  
21 comments? Thanks so much. We'll give you another  
22 30 seconds.

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1 MS. DIFILIPPANTONIO: Sure.  
2 So patients are calling into other doctors'  
3 offices and calling into hospitals to make sure  
4 that that patient is cared for, and feels like a  
5 human being, and not just thrown away in the trash,  
6 which is how most of us feel. So I leave you all  
7 with that.  
8 DR. MEYER: Thank you so much for your  
9 comments. We really appreciate them and the time  
10 coming here today to talk to us.  
11 Our next speaker is going to be speaker 14  
12 because speakers 11 through 13 were unable to  
13 confirm their participation for today.  
14 Speaker number 14, your audio should be  
15 connected now. Will you begin and introduce  
16 yourself? And please remember to state your name  
17 and any organization you are representing for the  
18 record.  
19 MS. NICHOLSON: Yes. Thank you. Hello. My  
20 name is Kate Nicholson. I am speaking on behalf of  
21 the National Council on Independent Living, the  
22 nation's largest cross-disability organization with

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1 centers in every state and territory, and the  
2 National Pain Advocacy Center, a new nonprofit that  
3 receives no industry funding and advocates for  
4 people in pain. I have no conflicts to disclose.  
5 Thank you for the opportunity to speak.  
6 Morphine milligram equivalents have become an  
7 increasingly important metric. For many pain  
8 patients, MMEs now determine what level of  
9 medication will be offered or covered, or even  
10 whether a patient will receive health care at all.  
11 For clinicians, MMEs can be a basis for oversight  
12 and a proxy for prescribing that falls outside  
13 standard practice or accepted norms. MMEs have  
14 become, in effect, a standard of care.  
15 Notably, there has been an uptick in  
16 tapering in patients whose MME falls outside dosage  
17 guidance in the 2016 CDC guideline for prescribing  
18 opioids for chronic pain. Ten to 12 recent  
19 observational studies paint a bleak picture of how  
20 opioid tapering is happening in practice, including  
21 that it often occurs abruptly with negative health  
22 consequences and that it may actually increase

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1 patient risk of overdose or suicide, in addition to  
2 destabilizing their lives.  
3 I hear from patients whose care has been  
4 limited, denied, or terminated due to MMEs almost  
5 daily. One woman with advanced MS wrote to me to  
6 say that she had led a full life on a steady dose  
7 of opioids for over ten years, but that her dosage  
8 was slightly above the MME recommended in the  
9 guideline. Since her doctor has terminated her  
10 medication, she has spent the last year entirely in  
11 bed.  
12 Another wrote, "My situation has become  
13 desperate, as my condition worsened. Sunday, I  
14 called a suicide hotline for the first time. My  
15 ability to work is drawing to a close. My marriage  
16 is in serious trouble. I'm sorry to be so dismal,  
17 but I am at the end of my rope."  
18 Forced and abrupt tapering continues despite  
19 warnings from the CDC, the FDA, and HHS. Given how  
20 consequential MMEs have thus become, we thank the  
21 FDA for hosting this session. Specifically, we  
22 underscore the concern that variations in drug

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1 metabolization, both among medications and from  
2 genetic variabilities, are insufficiently accounted  
3 for. Also, as one presenter will show, there are  
4 flaws in how MMEs are calculated in practice. The  
5 same medication given at the same interval could be  
6 calculated to have an MME that falls below and  
7 above the 50 to 90 threshold.

8 In closing, we ask that the FDA look closely  
9 at the scientific integrity, viability, and  
10 continued use of this concept because over-reliance  
11 on the MME metric, which is supposed to be used to  
12 ensure patient safety, has also proven detrimental  
13 to many patients and to patient-centered care.

14 Thank you.

15 DR. MEYER: Thank you very much, speaker  
16 number 14.

17 Speakers number 15 and 16 did not confirm  
18 their participation for today, so we will move on  
19 to speaker number 17.

20 Speaker number 17, your audio should be  
21 connected now. Please begin and introduce  
22 yourself. Please remember to state your name and

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1 any organization you are representing for the  
2 record.

3 MS. BROOKS: My name is Kelly Brooks, and I  
4 don't have any financial or conflicts to disclose.  
5 Again, my name is Kelly Brooks, and I'm a patient  
6 with reflex sympathetic dystrophy, rheumatoid  
7 arthritis, and stiff-person syndrome. I have been  
8 in pain management for 12 years. I have always  
9 struggled with getting the right amount of pain  
10 relief from my medication.

11 For a while, I can manage at my baseline  
12 level, at a 6, with my RSD. Unfortunately, I was  
13 diagnosed with RA a couple months ago, and now my  
14 baseline is an 8. My prescribed dosage does not  
15 help me if my pain increases due to activity,  
16 flares, or being diagnosed with another disease. I  
17 need more medication for those intolerable pain  
18 levels, not less. I shouldn't have to cry in bed  
19 because I went to watch my son participate in a  
20 single sports event. I deserve to participate in  
21 life, and I didn't ask for any of these diseases.

22 For many years, my doctor and I have faced

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1 increased pressure to reduce my medication, and MME  
2 limits have kept my doctor from being allowed to  
3 increase my medication to an effective range. I  
4 have led a support group for ten years online for  
5 thousands of women with RSD. I hear my story  
6 repeated all over the country daily. I watched my  
7 own mother with MS struggle with not getting the  
8 right amount of medication she needed.

9 Recently, our support group lost 5 patients  
10 in 7 days to suicide, all of them directly related  
11 to not being able to get medication or being  
12 forced-tapered off their current prescriptions. I  
13 knew all of them, and the hardest suicide for me  
14 was my friend's young son, Danny Lucas, who was  
15 never even given pain meds due to MME and CDC  
16 guideline, and he still committed suicide because  
17 he couldn't handle the pain.

18 I truly don't believe there is a future  
19 direction for MME. MME is a crazy thought, just a  
20 thought. It's fundamentally broken and you can't  
21 fix it. It can't be refined or improved by  
22 tinkering. MME limits need to be fully repealed,

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1 both federally and at state level. It needs to  
2 start over from the ground up with reasonable pain  
3 management and reasonable guidelines. I believe  
4 pain management doctors actively practicing  
5 medicine should be making the decisions, not  
6 doctors behind a desk at the FDA or CDC.

7 Pain management is not a one-plan-fits-all  
8 treatment. Patients are people. People are  
9 different. I will provide a quick example with  
10 aspirin. If a 7-foot-4 basketball player takes  
11 2 aspirin and a 4-foot-5 little person takes  
12 2 aspirin, the little person has 4 times the amount  
13 of aspirin in their system.

14 Did the little person take too much aspirin  
15 or did the basketball player take too little? Our  
16 bodies respond, metabolize, and ingest medication  
17 differently. Basing our treatment on MME is  
18 disgusting, it's barbaric, and it's quite obviously  
19 causing a problem with pain patients and pain  
20 management.

21 In closing, I just would like to say that  
22 pain management that is done by actual pain



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1 management doctors and not primary care physicians  
2 is extremely scrutinized. We are randomly drug  
3 tested. I can be called at any point and be asked  
4 to bring in my medication and have my pills  
5 counted. All my medication is sent electronically  
6 to the pharmacist, so I don't know how true pain  
7 management patients are even part of or being  
8 considered as a loophole to the opioid crisis.  
9 Thank you very much for your time. I  
10 appreciate the FDA allowing me the moments to  
11 speak, and I hope, for our sakes, you can hear our  
12 plea. We are in desperate need of help. Thank  
13 you.  
14 DR. MEYER: Thank you for your comments,  
15 speaker 17.  
16 Speaker number 18 did not confirm their  
17 participation for today, so we will move on to  
18 speaker number 19.  
19 Speaker number 19, your audio should be  
20 connected now. Please begin and introduce  
21 yourself, and remember to state your name and any  
22 organization you're representing for the record.

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1 DR. ARORA: Hi. Am I audible? Hello?  
2 Hello?  
3 DR. MEYER: Hi. We can hear you.  
4 AV TECH: Yes, we can hear you.  
5 MR. ARORA: Hi. My name is Rahul Arora, and  
6 I'm a postgraduate in palliative medicine from  
7 India. These are my credentials. I think the  
8 discussion that we're having is important to  
9 discuss this right now. I have no conflicts of  
10 interest.  
11 I think we already know about the existing  
12 guidelines and what they say. What I am  
13 concerned -- and I'm going to take a very different  
14 route from what others have said, and this might  
15 disturb all these champions who continue to fight  
16 against pain. But the fact is that I am deeply  
17 concerned by the use of opioids that I see around  
18 myself and the exclusion of opioids, which is not  
19 proceeding according to plan.  
20 I just saw a patient being escalated from  
21 5 mg q4 hourly to 20 mg q4 hourly in one instance,  
22 and I am concerned that guidelines are not being

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1 followed. I am not saying that we do not need to  
2 use opioids. I know that there are no options,  
3 especially in pain conditions like cancer pain,  
4 chronic degenerative neurological illnesses, but we  
5 also need to be very forthright about discussing  
6 their drawbacks. We need to be in a position where  
7 we can talk to the patients directly about the  
8 impact of opioids on survival and the impact of  
9 opioids on, say, the addiction potential of  
10 opioids. We need to investigate that, too.  
11 The broad elements of my presentation  
12 include whether we need to be including any NSAIDs.  
13 There was a talk about atypical opioids, so talking  
14 about NSAIDs, when I prescribe opioids and patients  
15 are getting NSAIDs, I need a conversion.  
16 Whether opioids have an adverse effect on  
17 survival, we do not usually account for incomplete  
18 cross-tolerance, which is very disturbing, and  
19 there is a lack of options for treatment of acute  
20 neuropathic pain, and this could be a reason why  
21 opioids are being used indiscriminately.  
22 There is oral morphine sulfate that we use,

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1 then inclusion of NSAIDs, spoken about this  
2 earlier. There is increasing evidence which talks  
3 about the adverse effects of opioids on survival,  
4 and these are studies by Boland, et al. and  
5 Hasegawa, et al., which say directly that opioids  
6 have an adverse impact on survival.  
7 Can we ignore that impact? These are the  
8 difficulties with using available options for  
9 neuropathic pain, like lack of cardiac monitors in  
10 my ward, like the use of midazolam with ketamine  
11 for emergence delirium, or the indiscriminate used  
12 increments in morphine.  
13 One of the practical issues is inability to  
14 account for incomplete cross-tolerance and  
15 conversion between various routes of  
16 administration. We talk about MED. We usually  
17 talk about the oral MED and not the IV or the  
18 subcutaneous routes.  
19 Evaluation of complexity of pain control in  
20 association with descriptors of difficult-to-  
21 control pain on scales such as CHMP that fails to  
22 reveal a linear correlation, and there is limited

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1 availability of options for breakthrough pain  
2 management when transdermal fentanyl is being used  
3 for background baseline pain. So number of doses  
4 before dose escalation is to be achieved needs to  
5 be considered more thoroughly.  
6 We know that when we use rapidly acting oral  
7 fentanyl preparations or rapid onset opioids, they  
8 might not be oral always, but intranasal  
9 formulations, let's say buccal formulations, and  
10 when we're using morphine for breakthrough  
11 pain -- so when we use IROs versus morphine for  
12 breakthrough pain, can we actually equate the  
13 concept of morphine equivalent daily dosage?  
14 What are the future directions? We should  
15 study opioid dependence in advanced cancer. We  
16 should study the role of interventional pain  
17 procedures, which then leads to a decrease in  
18 opioid doses in the long term; what is the impact  
19 on opioids on survival; and we should investigate  
20 this as a primary outcome. We should also be  
21 studying, in turn, variation pharmacokinetics,  
22 which has been demonstrated very clearly in this

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1 particular seminar.  
2 I would like to thank you for your time, and  
3 I would like to thank the FDA for this opportunity  
4 to present.  
5 DR. MEYER: Thank you very much, speaker  
6 number 19.  
7 Speaker number 20 did not confirm their  
8 participation for today, so we will move on to  
9 speaker 21.  
10 Speaker 21, your audio should be connected  
11 now. Please begin and introduce yourself, and  
12 please remember to state your name and any  
13 organization you are representing for the record.  
14 (No response.)  
15 DR. MEYER: Speaker number 21, can you hear  
16 us?  
17 MS. WEISMAN: Yes. Can you hear me?  
18 DR. MEYER: We can. Please go ahead.  
19 Remember to state your name and organization you  
20 are representing for the record.  
21 MS. WEISMAN: Okay. Great. My name is  
22 Wendy Weisman, and I'm not representing and don't

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1 have any conflicts. I just want to say thank you  
2 for giving me this opportunity. I'm grateful our  
3 voices will finally be heard and attention is being  
4 brought to this crucial topic.  
5 The MME number I feel was originally  
6 assigned with a patient in mind that has never been  
7 on narcotics, has no health conditions that affect  
8 metabolizing medications or tolerance, and for  
9 patients who will only be on narcotics short term  
10 for an acute injury. This unreasonable expectation  
11 has destroyed many chronic pain patients' treatment  
12 plans. Here's just some of my stories summarized.  
13 I'm a 34-year-old RN. I've worked hands on  
14 with patients since I was 18. As my body broke  
15 down and pain progressed, I took a desk job as an  
16 RN with an orphan drug program until I collapsed in  
17 the middle of the office. I've been officially  
18 deemed permanently disabled, and I'm now fighting  
19 for quality of life while dealing with crippling  
20 pain. I have CRPS or RSD, also known as the  
21 suicide disease, and Ehlers-Danlos syndrome. These  
22 are labeled as two of the most painful conditions.

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1 I was a compliant patient only seeing one  
2 physician until my MME score was flagged too high.  
3 The 7-plus years of monthly clean drug screens,  
4 being on one medication with no increase or change  
5 in dose; nothing mattered. I was told on a routine  
6 appointment that I had failed my drug screen and  
7 was being released. The doctor eventually  
8 retracted and said it was a false positive, but it  
9 was too late.  
10 Not only did I lose continuity of care with  
11 my physicians, but this flagged me as a high-risk  
12 patient. Physicians didn't care that it was false;  
13 I was a risk, especially with my MME score. Many,  
14 including doctors and staff, unfairly labeled and  
15 judged me as a drug seeker because of the score.  
16 One physician actually said she would like to help  
17 me, but she couldn't because of my score. She  
18 added that if she were me in that level of pain she  
19 knows that I'm in, she would want to die.  
20 This is what pain patients go through. We  
21 are judged unfairly and end up with greatly reduced  
22 quality of life. This is why many choose suicide.

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1 As you're hearing over and over again, we lose  
2 people every day.  
3 My pain is still not managed. My quality of  
4 life is poor. Please consider making changes.  
5 Please hear our voices. Please consider the actual  
6 patients and life that we could have. Quality of  
7 life can't be quantified in a number. Thank you.  
8 DR. MEYER: Thanks very much, speaker 21.  
9 Speaker 22 did not confirm their  
10 participation for today, so we will move on to  
11 speaker number 23.  
12 Speaker 23, your audio should be connected  
13 now. Please begin and introduce yourself, and  
14 remember to state your name and any organization  
15 you're representing for the record.  
16 (No response.)  
17 DR. MEYER: Hi. Speaker 23, can you hear  
18 us?  
19 (No response.)  
20 DR. MEYER: Speaker number 23, we're having  
21 trouble hearing you, so we're going to move on to  
22 the next speaker for now and will return to you

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1 later.  
2 The next speaker is speaker number 24.  
3 Speaker number 24, your audio should be  
4 connected now. Please introduce yourself.  
5 Remember to state your name and any organization  
6 you are representing for the record.  
7 (No response.)  
8 DR. MEYER: Speaker number 24, can you hear  
9 us?  
10 (No response.)  
11 DR. MEYER: Okay. Speaker number 24, we're  
12 having trouble hearing you, so we will move on to  
13 the next speaker and try and return to you later in  
14 the session.  
15 The next speaker should be speaker 25.  
16 Speakers 25, your audio should be connected.  
17 Will you please begin and introduce yourself? And  
18 state your name and any organization you're  
19 representing for the record.  
20 (No response.)  
21 DR. MEYER: Okay. Speaker 25 --  
22 DR. GHEI: Yes. I'm Nita Ghei. If I can

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1 have my slides, please?  
2 Good afternoon. Thank you for the  
3 opportunity to participate in this workshop. I am  
4 Dr. Nita Ghei. I'm the director of research of  
5 headsUP Migraine, and I have no conflicts to  
6 disclose.  
7 The main points I would like to make today  
8 are, first, the current use of MME conflates pain  
9 with disease, and it ignores the vast array of  
10 diseases and conditions that actually cause chronic  
11 pain. The use of MME by law enforcement that  
12 limits overdose deaths by tracking medical users  
13 and the physicians is destined to fail because the  
14 vast majority of overdose deaths is polypharmacy  
15 and associated with street drugs. Medically  
16 fragile patients and the physicians are the  
17 collateral damage of this misapplication of the  
18 MME.  
19 The MME was designed for titration of dose  
20 for individual patients. The MME takes into  
21 account the wide variations of patients, the level  
22 of pain, response to medication, weight, and so

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1 forth. Ethically, MME should be used to determine  
2 the optimal outcome and care plan for the patient.  
3 Instead, far too many agencies have grabbed  
4 on the CDC's 2016 guideline as hard rules. 90 MME,  
5 and even 50, have become the magic numbers. The  
6 CDC's judgment replaces that of the physician.  
7 Worse, with law enforcement tracking opioid  
8 prescriptions using MME and the threat of active  
9 forfeiture always present, it's safer for  
10 physicians to either taper to 90, or even 50, or  
11 simply decline to write prescriptions for opioids  
12 altogether.  
13 Millions of sick Americans with chronic and  
14 progressive diseases have been medically abandoned.  
15 For a year, I was one of the abandoned, too. The  
16 current use of MME-treating physicians to treat  
17 patients is identical to the detriment. Different  
18 diseases and conditions all should be factors in  
19 determining a treatment plan. A universal 90 or  
20 50 MME severely limits the physician's ability to  
21 do so.  
22 Worse, however, is law enforcement state

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1 agencies tracking physicians by MME without  
2 context. Certain kinds of physicians will write  
3 more opioid prescriptions. Relying on MME by law  
4 enforcement fails to account for this. The  
5 resulting rates can disrupt care for thousands of  
6 patients.  
7 The variance in opioids is conflation. The  
8 vast majority of overdose deaths are the result of  
9 alcohol and polypharmacy, mostly street drugs.  
10 Overdose deaths have increased even as opioid  
11 prescription numbers have fallen steadily since  
12 2012. The actual numbers of patients who have  
13 prescription who overdose are very low, about  
14 4 [indiscernible] percent in North Carolina to just  
15 over 1 percent in Massachusetts.  
16 Pain patients are not the population where  
17 the bulk of overdoses are occurring. There's no  
18 evidence using MME to persecute treating physicians  
19 and pain patients will significantly reduce  
20 overdose deaths. Widening naloxone availability  
21 would be far more effective. Pain patients and the  
22 physicians are collateral damage in the opioid

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1 crisis. Returning MME to scientific  
2 evidenced-backed growth [indiscernible] would be a  
3 step in the right direction. Thank you.  
4 DR. MEYER: Thank you very much, speaker  
5 number 25.  
6 We are going to try and go back to speaker  
7 number 23.  
8 Ms. Stewart, are you able to speak so we can  
9 make sure we can hear you?  
10 MS. STEWART: I believe so. I think I  
11 figured it out this time.  
12 DR. MEYER: Ah. We can hear you. Great.  
13 Okay. Please go ahead and introduce yourself.  
14 Remember to state your name and any organization  
15 you are representing for the record.  
16 MS. STEWART: Alright. Thank you. My name  
17 is Tamera Stewart. I'm the national policy  
18 director for the P3 Alliance. We calculate that  
19 21 to 26 percent of the American population would  
20 not be expected to respond, quote, "normally" to  
21 doses that are being incorrectly interpreted as  
22 limits in the CDC guideline, based solely on

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1 genetic makeup.  
2 No other part of our government would  
3 knowingly regulate or discriminate against a  
4 quarter of Americans based on their DNA. We do not  
5 allow employers or insurance companies to treat  
6 customers differently based on genetic information,  
7 yet this is exactly what's happening in medicine.  
8 Just this morning, Dr. Hayden [ph] spoke on  
9 pharmacogenomics and mentioned the populations from  
10 around the world have expected variations in  
11 specific CYP activities. My calculations on the  
12 population, excluded by the CDC guideline, were  
13 based on that same concept, extrapolated using the  
14 known percent of estimated frequency in each  
15 variant within each ethnic population in the U.S.  
16 We all know that tolerance, health of  
17 organs, comorbidities, et cetera, all impact  
18 efficacy and the safety of pain medications. The  
19 P3 Alliance feels that any guideline or given  
20 definition of MME that doesn't account for these  
21 and other factors is falling short and even risks  
22 stepping into discriminatory medicine.

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1 No matter who sets that normal dose or how  
2 it's calculated, because of known variations, it's  
3 impossible to account for everyone. If recent  
4 reductions in prescribing were a valid solution and  
5 deserved to be celebrated as they are, many of the  
6 patients who were cut off or tapered to ineffective  
7 doses wouldn't still be suffering or further  
8 destabilizing.  
9 None of today's presentations focused on  
10 reductions and prescribing mentioned tracking the  
11 patient outcomes. How are the veterans actually  
12 doing? When we speak to large groups of vets,  
13 their interpretation on how they're doing is  
14 considerably different.  
15 It's obvious that desired positive outcome  
16 metrics are not universal, but it seems few ever  
17 include what the patient really views as important.  
18 It's common, even though we claim the entirety of  
19 medicine is about treating patients individually.  
20 If inflexible guidelines, algorithms, and  
21 definitions based on an imperfect concept of MME  
22 are continued to be allowed, we'd like to ask the

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1 FDA to require tracking to learn if the given MME,  
2 or how it's being defined, is effective according  
3 to positive outcome metrics that actually matter to  
4 the patients.  
5 Knowing that as many as 21 to 26 percent of  
6 Americans don't respond, quote, "normally," any  
7 official action taken by government agencies or  
8 state or local governments attempting to  
9 standardize anything with opioids must include a  
10 way to ensure that that variability is being  
11 accounted for. Thank you.  
12 DR. MEYER: Thank you very much, speaker  
13 number 23.  
14 Let's try speaker number 24 again. Can you  
15 hear us?  
16 MS. FUQUA: I can hear you. Can you hear  
17 me?  
18 DR. MEYER: Yes. You sound great.  
19 MS. FUQUA: Okay. Great.  
20 DR. MEYER: Your audio's connected, so you  
21 can go ahead and state your name and any  
22 organization you're representing for the record,

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1 and start your presentation. Thank you.  
2 MS. FUQUA: My name is Anne Fuqua. I'm a  
3 member of the National Pain Advocacy Center's  
4 Community Advisory Council and assist with  
5 CSI:OPIOIDS, a pilot study that seeks to examine  
6 suicides in patients with chronic pain.  
7 The morphine milligram equivalent was  
8 originally intended to serve as a means to roughly  
9 compare the effects of various members of the  
10 opioid class of medications to what was mentioned  
11 as the gold standard, opioid, morphine. MME was  
12 never intended to function as an indicator of  
13 quality care, [indiscernible – audio distorted], or  
14 a threshold [indiscernible]. Yet, MME is now  
15 commonly used in each of these situations, as well  
16 as numerous others, though it was never intended.  
17 I am so grateful for the many professionals  
18 who have spoken so forcefully on this subject  
19 today. Morphine milligram equivalents has been  
20 [indiscernible] CDC guideline. The impact on  
21 patients have been both widespread and  
22 [indiscernible]. As a chronic pain patient with

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1 multiple CYP cytochrome 450 [indiscernible], I've  
2 experienced many of the problematic issues related  
3 to MME described by Drs. McPherson and Fudin.  
4 Doses that would be both unnecessary  
5 [indiscernible] allow me to enjoy a good quality of  
6 life. My overall health has dramatically improved.  
7 I live in a city with some of the finest healthcare  
8 providers in the nation, yet I must fly across the  
9 country every three months just to get medical care  
10 and maintain the quality of life I now have.  
11 [Indiscernible] of medical care is an ever  
12 present concern that should not even be a  
13 consideration in the 21st century in the United  
14 States of America. An MME above 90 in a patient  
15 who is stable and functioning well without  
16 considerable risk is somewhat like a false alarm.  
17 This can lead to involuntary tapers, which elevates  
18 the risk to patients, and in fact results in actual  
19 harm, even death.  
20 A lower MME can provide a false sense of  
21 security even when [indiscernible]. An example of  
22 this could be a physician that prescribed codeine

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1 [indiscernible] opioids. However, he is unaware  
2 that his patient has a CYP450 2D6. Also, providers  
3 should be able to focus on their patients, their  
4 pain, and the manner in which their pain impacts  
5 the patient's ability to function. In the current  
6 policy environment, having to focus on MME  
7 [indiscernible] and the real issues that the  
8 patient is experiencing. Thank you.  
9 DR. MEYER: Thanks very much, speaker 24.  
10 Speakers 26 and 27 did not confirm their  
11 participation for today, so we will now go to  
12 speaker number 28.  
13 MS. STIESS: Hello? Can you hear me?  
14 DR. MEYER: Yes. Your audio is connected.  
15 We can hear you. So ahead and introduce yourself.  
16 State your name and any organization you are  
17 representing for the record.  
18 MS. STIESS: Hello. My name is Samantha  
19 Stiess. I am representing myself today. I have no  
20 financial issues or [indiscernible – audio  
21 distorted].  
22 Thank you for letting me speak. My voice is

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1 quiet, but it will be heard today. I've been  
2 suffering from eight chronic pain diseases,  
3 including RSD, tardive dyskinesia, polycystic  
4 ovarian syndrome, [indiscernible] cultures, chronic  
5 migraine, depression, and anxiety since I was  
6 15 years old. I'm now 35. I don't remember one  
7 day that I was well. I've tried everything from  
8 [indiscernible] naturally: physical therapy,  
9 cortisone shots; trigger blocks, and  
10 [indiscernible], and I started to get one more  
11 block at 16.

12       Once you've been diagnosed with a lifelong  
13 chronic pain illness, you don't get narcotics and a  
14 pat on your back. You try every step possible, but  
15 you don't have them until you have no options left.

16       At 21, I've had two botched spinal cord  
17 stimulators that made my disease spread throughout  
18 my entire body. Something that was promised to  
19 give my life back took it away even more, caused  
20 permanent harm and damage, and it wasn't a narcotic  
21 pain medication.

22       At 28, I found my [indiscernible] dose of

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1 medication and my third spinal cord stimulator to  
2 keep me looking like a semi-normal human being. I  
3 was able to do everything with my husband, even  
4 lose 75 pounds because, yes, it took 12 to 15 years  
5 to find that perfect dose.

6       I also get violently ill from  
7 [indiscernible] narcotic pain medication, because  
8 you have to realize, no one chooses this. All the  
9 NSAIDs, biopsies, and Celebrexes led me to a  
10 stomach ulcer at 16 years old, and I never fully  
11 got better at 35.

12       I never failed a drug test. I did  
13 everything I was told, even to recently getting a  
14 pain pump because doctors are too scared to write  
15 an oral prescription, but have absolutely no issue  
16 cutting your body open and putting other implants  
17 in you at all for the sake of not losing their  
18 license. With no extra pain medication after  
19 surgery, if the pump doesn't work, they will still  
20 take your medication away and go, "Tough luck."  
21 How crazy does that sound?

22       Five years ago, my life was taken away from

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1 bulky agendas and misinformation by the CDC, PROP,  
2 and the DEA. I lost my best pain management doctor  
3 who gave me my life back and my pain medication to  
4 let me function like a normal human being. If you  
5 know what it's like to lose your life over and over  
6 again, you would understand exactly how we feel.

7       I purposely [indiscernible] individuals with  
8 absolutely no science backup [indiscernible]. PROP  
9 and the CDC are exactly the boy who cried wolf.

10 There isn't an opioid crisis, however, there is an  
11 illegal fentanyl and heroin crisis from drug  
12 addicts, not chronic pain sufferers, in our country  
13 because all agencies want to pigeonhole us together  
14 and not realize our care. Bad drug addicts will  
15 always find a way to get high and make all of you  
16 look like a bunch of fools.

17       Chronic pain patients just want their life  
18 back. With regulated narcotic pain medication we  
19 got from our pharmacies, we never got high off  
20 medication. We just want to live a life that was  
21 semi-normal for us, and we can't even have that  
22 now.

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1       Can you tell me you guys know the difference  
2 between a drug addict and a chronic pain patient  
3 after five years that you tortured and that you've  
4 bestowed upon us? This is a human rights  
5 violation. We know it. We deserve better than  
6 this hand that we've dealt with. We need to go  
7 after PROP and the CDC and the DEA for immoral drug  
8 [indiscernible] human rights violation.

9       I lost my life, but I'm speaking out on the  
10 people who can't take one more day of their pain,  
11 and under their advice [indiscernible] narcotic  
12 pain medication with. I've been on [indiscernible]  
13 for five years. I have now an 11-month-old baby  
14 that I have to take care of. My blood pressure is  
15 going through the roof because my pain is not  
16 controlled or stabilized anymore.

17       My 75 pounds I once lost is piling back up.  
18 My high-risk pregnancy, I almost didn't make it out  
19 alive. I hemorrhaged. After my C-section, I  
20 needed two blood transfusions. I still wasn't  
21 given anything extra but ibuprofen, and that was  
22 blood. Smart, right?

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1 I see the number of overdoses especially  
2 increasing since COVID. Pharmaceuticals have been  
3 decreasing heavily for five years since PROP, and  
4 its doctors who aren't pain management doctors at  
5 all, and have no business deciding our fate, and  
6 who went and destroyed the chronic pain patient's  
7 way of life and not help the drug addicts' life at  
8 all, mentally or physically.  
9 Why do we hear one side of the story from  
10 the media? What are you going to do to fix this?  
11 Why don't you realize it's illegal fentanyl and  
12 heroin on the street killing drug addicts, not  
13 chronic pain patients that are committing suicide  
14 rather than going out on the street?  
15 Can all the big corrupted agencies know the  
16 difference between chronic pain patients, who are  
17 dropping like flies because you took our only  
18 lifeline away, but absolutely --  
19 DR. MEYER: Speaker 28?  
20 MS. STIESS: Yes?  
21 DR. MEYER: I'm sorry. Your time is up.  
22 Can you please just wrap up your comments? Thank

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1 you.  
2 MS. STIESS: Yes. Kale, yoga, and Tylenol,  
3 and prayers aren't going to do anything for us,  
4 who've already tried everything possible to stop  
5 our pain. Thank you so much for your time.  
6 DR. MEYER: Thanks very much, speaker 28.  
7 Speaker numbers 29 and 30 were unable to  
8 confirm their participation for today, so we will  
9 now move to speaker number 31.  
10 Speaker number 31, your audio should be  
11 connected. Please begin and introduce yourself,  
12 and remember to state your name and any  
13 organization you're representing for the record.  
14 MS. CORLEY: Hi. My name is Donna Corley,  
15 and I'm the director of ASAP or Arachnoiditis  
16 Society for Awareness and Prevention. Thank you on  
17 behalf of millions of chronic pain patients living  
18 with rare, debilitating diseases such as adhesive  
19 arachnoiditis, Tarlov cyst disease, EDS, eRPS, just  
20 to name a few.  
21 When the 2016 CDC guideline were  
22 implemented, not one part of it was considered for

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1 patients who suffered with rare disease or who have  
2 metabolic issues such as being a poor or rapid  
3 metabolizer of opioid medications with regards to  
4 the MME dosage restriction. This issue was brought  
5 to the CDC's attention many times by myself and  
6 others to no avail.  
7 As an advocate, I always believed there was  
8 equality for everyone, regardless of race, sex,  
9 religion, or even social status. Sadly, this has  
10 not been the case for those of us who suffer with  
11 these intractable pain diseases. In fact, we have  
12 received just the opposite and been ostracized,  
13 stigmatized, traumatized, and left by the wayside  
14 without care of any kind by physicians who were too  
15 afraid of state and federal regulations to offer or  
16 continue treatment that many patients have been  
17 receiving successfully prior to the implemented CDC  
18 guideline.  
19 What has happened to pain patients since  
20 2016 has been nothing short of tragic: forced  
21 tapering of their medications; forced withdrawal;  
22 loss of their stable medications; loss of their

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1 physicians; loss of jobs and livelihood, causing  
2 many to seek disability and Medicaid; uncontrolled  
3 pain, causing many to seek suicide as the only  
4 viable solution left to them to end their torturous  
5 agony, all thanks due to the MME dosage threshold  
6 based on faulty science, lacking any sound  
7 consensus among numerous experts, including the CDC  
8 authors themselves and the -- [inaudible – audio  
9 lost].  
10 DR. MEYER: Speaker 31, I lost you.  
11 (No response.)  
12 DR. MEYER: Can you try and say something  
13 again?  
14 (No response.)  
15 DR. MEYER: Okay. I think we're having some  
16 technical difficulties. Just give us a minute to  
17 try and work it out.  
18 (Pause.)  
19 DR. MEYER: Okay. Just bear with us. We're  
20 having some technical difficulties. We want to  
21 give the speaker time to call back in. Thank you.  
22 MS. CORLEY: Hello?

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1 DR. MEYER: Hi. Is that Donna?  
2 MS. CORLEY: Hi -- AMA went on to  
3 say [inaudible – audio gap] -- I'm echoing.  
4 DR. MEYER: Hi. I just want to remind  
5 people to mute their phones, And if you're  
6 listening through computer audio while you're  
7 speaking, make sure your computer audio is turned  
8 down all the way.  
9 Okay. Try again.  
10 MS. CORLEY: The truth of the matter is that  
11 the MME threshold remains a hard policy by many  
12 health insurers, pharmacies, and state medical  
13 boards. The AMA strongly urged the CDC to add  
14 language to the revised CDC guideline, urging those  
15 entities to rescind these policies given the  
16 absence of data to suggest a relationship between  
17 the arbitrary threshold and improved patient  
18 outcomes, as well as the harms done to patients as  
19 a result of inappropriate tapering or denial of  
20 care.  
21 The FDA has the opportunity to undo the  
22 massive harms of millions of pain patients all

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1 across the country. On behalf of all those who  
2 couldn't be here to speak for themselves today,  
3 we're begging you to do the right thing and stop  
4 this devastation. Thank you.  
5 DR. MEYER: Thank you very much, speaker 31.  
6 Speakers 32 through 35 were not able to join  
7 today or did not confirm their participation, so  
8 this is the end of the public comment session.  
9 The public comment session of the workshop  
10 is now concluded. Information on how to submit to  
11 the docket for any remaining comments are being  
12 shown on the screen right now. We understand that  
13 the virtual meeting format may have made it  
14 challenging for some people to participate in the  
15 public comment session today, but we really truly  
16 want to hear from you. If you have any additional  
17 comments that you are unable to submit or to speak  
18 about today, please submit them to the docket. If  
19 you have problems with submitting to the docket,  
20 reach out to us so that we can help you. We truly  
21 do consider these submissions carefully along with  
22 the rest of the meeting materials.

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1 I want to sincerely thank all of the public  
2 comment session speakers for sharing your  
3 experiences and your insights on this topic. The  
4 comments we have heard today will be carefully  
5 considered by the FDA and the panel in the  
6 discussion tomorrow.  
7 I'm now going to turn the meeting back over  
8 to Dr. Chai for any closing comments.  
9 Closing Remarks – Grace Chai  
10 DR. CHAI: Thank you, Dr. Meyer.  
11 Before we adjourn, I'd also like to thank  
12 all the meeting participants today, from the  
13 speakers for their excellent presentations, as well  
14 as the panelists for questions, and a very special  
15 thank you to those who spoke during the public  
16 comment session. We hear you. As Dr. Meyer said,  
17 patients and public health are our priority and  
18 reinforce why we are meeting to discuss the  
19 science.  
20 As Dr. Meyer stated, the public docket, as  
21 cited in the Federal Register notice, will be open  
22 through August 9, 2021 for your feedback. You are

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1 encouraged to post further comments there. And as  
2 a gentle reminder, meeting materials, including the  
3 agenda for day 2 and the panel discussion  
4 questions, are posted on the meeting website.  
5 Thank you again to all participants and to  
6 the audience for attending today. We look forward  
7 to reconvening tomorrow at 9 a.m. Eastern Daylight  
8 Time to continue this important scientific  
9 workshop. We will now adjourn the meeting. Thank  
10 you for your participation.  
11 (Whereupon, at 4:21 p.m., the meeting was  
12 adjourned.)  
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