

FDA Public Virtual Scientific Workshop - Day 2
Morphine Milligram Equivalents

June 8, 2021

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 2</p> <p>14</p> <p>15</p> <p>16 Tuesday, June 8, 2021</p> <p>17 9:00 a.m. to 4:50 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>

<p style="text-align: right;">Page 9</p> <p style="text-align: center;">C O N T E N T S</p> <p>1</p> <p>2 AGENDA ITEM</p> <p>3 Welcome</p> <p>4 Introductions, Speakers and Panelists</p> <p>5 Grace Chai, PharmD 11</p> <p>6 Recap of Day 1 and Introduction to Day 2</p> <p>7 Grace Chai, PharmD 13</p> <p>8 Opioid Conversion Information in</p> <p>9 Approved Labeling</p> <p>10 Mary Therese O'Donnell, MD, MPH 21</p> <p>11 Nonclinical Pharmacology and Toxicology</p> <p>12 Considerations Regarding Opioid</p> <p>13 Comparisons and Risk Assessments</p> <p>14 (Basic Opioid Pharmacology 101)</p> <p>15 Daniel Mellon, PhD 31</p> <p>16 MME Calculations and Abuse Liability</p> <p>17 Considerations</p> <p>18 Chad Reissig, PhD 70</p> <p>19 Clarifying Questions to Speakers</p> <p>20 Grace Chai, PharmD 90</p> <p>21</p> <p>22</p>	<p style="text-align: right;">Page 11</p> <p style="text-align: center;">P R O C E E D I N G S</p> <p>1 (9:00 a.m.)</p> <p>2 Welcome and Introductions</p> <p>3 DR. CHAI: Good morning and welcome back.</p> <p>4 Thank you for joining us virtually for day 2 of</p> <p>5 this Public Scientific Workshop on Morphine</p> <p>6 Milligram Equivalents. I would first like to</p> <p>7 remind everyone to please mute your line when you</p> <p>8 are not speaking.</p> <p>9 My name is Grace Chai, and I am the</p> <p>10 associate director for Special Initiatives in the</p> <p>11 Office of Surveillance and Epidemiology under the</p> <p>12 Center of Drug Evaluation and Research here at FDA,</p> <p>13 and I will be chairing this meeting.</p> <p>14 First, I would like to start with a few</p> <p>15 housekeeping details. Meeting materials, including</p> <p>16 the agenda, the list of speakers, panelists' names</p> <p>17 and disclosures are available online and posted on</p> <p>18 the meeting website. Yesterday, we went through</p> <p>19 panelists' and participants' introductions. Today,</p> <p>20 I will refer you to the panelists' names and</p> <p>21 disclosures on the meeting materials website.</p> <p>22</p>
<p style="text-align: right;">Page 10</p> <p style="text-align: center;">C O N T E N T S (continued)</p> <p>1</p> <p>2 AGENDA ITEM</p> <p>3 Oral and Intravenous Oxymorphone:</p> <p>4 Relative Potency Compared to Other</p> <p>5 μ Opioid Agonists in Humans</p> <p>6 Shanna Babalonis, PhD 110</p> <p>7 Opioid Potency: Pharmacological and</p> <p>8 Non-Pharmacological Factors</p> <p>9 Sandra Comer, PhD 131</p> <p>10 Inches, Centimeters, and Yards:</p> <p>11 Overlooked Definition Choices Inhibit</p> <p>12 Interpretation of Morphine Equivalence</p> <p>13 Nabarun Dasgupta, MPH, PhD 140</p> <p>14 Clarifying Questions to Speakers</p> <p>15 Grace Chai, PharmD 168</p> <p>16 Panel Discussion</p> <p>17 Judy Staffa, PhD, RPh 174</p> <p>18 Jennifer Nadel, MD 181</p> <p>19 Closing Comments</p> <p>20 Grace Chai, PharmD 331</p> <p>21</p> <p>22</p>	<p style="text-align: right;">Page 12</p> <p>1 The public docket as cited in the Federal</p> <p>2 Register notice will be open through August 9, 2021</p> <p>3 for your feedback. You are encouraged to post</p> <p>4 further comments there. The first break today will</p> <p>5 occur around 11 a.m. Lunch is scheduled for</p> <p>6 12:30 p.m., if you could plan accordingly.</p> <p>7 Our goal today is that this meeting will be</p> <p>8 a fair and open forum for discussion of these</p> <p>9 issues and that individuals can express their views</p> <p>10 without interruption. Thus, as a gentle reminder,</p> <p>11 individuals are asked to mute and unmute to speak</p> <p>12 only when recognized by me or other moderators to</p> <p>13 help facilitate this virtual meeting.</p> <p>14 During this meeting, only panel members,</p> <p>15 consisting of all invited speakers and panelists,</p> <p>16 will be able to ask clarifying questions of the</p> <p>17 presenters and participate in the panel discussions</p> <p>18 today. We have scheduled clarifying question</p> <p>19 sessions following groups of presentations. We</p> <p>20 encourage all panelists to jot down any clarifying</p> <p>21 questions you may have for presenters, and please</p> <p>22 take note of the times for the clarifying</p>

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1 questions.

2 As a gentle reminder, I'd like to remind all

3 the presenters and panelists that the arrows on the

4 screen, if you could refrain from touching the

5 arrows on the screen unless you are actively

6 presenting, as it will change the view for the

7 entire audience. So please refrain from touching

8 the arrows on the screen unless you are actively

9 presenting.

10 I will now try to provide a recap of day 1.

11 Can you hear me? Is the audio not coming

12 out that good?

13 AV TECH: I think we can hear you fine.

14 Recap of Day 1 and Introduction of Day 2

15 DR. CHAI: Okay. I'll keep going.

16 I will now try to provide a recap of day 1.

17 The presentations yesterday were excellent and

18 provided us a wealth of information. Although I

19 don't know if I can do them justice, I will now try

20 to briefly summarize what we heard yesterday.

21 We started the day with opening remarks from

22 Dr. Cavazzoni, the director for CDER here at FDA.

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1 She spoke of the difficulties of this past year,

2 particularly for patients, and that stronger

3 science is needed to better utilize MMEs to ensure

4 appropriate dosing and to prevent overdoses.

5 Conversion factors have great complexities and may

6 have a role.

7 Next, I touched upon the different topics

8 that will be presented by other speakers. An

9 influence diagram was used to illustrate the

10 complexities and how we cannot look at different

11 components in a silo. Rather, it all starts with

12 the science, and I described the resulting

13 influences of science through the multiple

14 applications and how they may ultimately impact

15 patients. The opioid crisis is highly complex, and

16 even with MMEs, there are many moving parts and

17 should not be considered in isolation.

18 Ms. Cowan spoke next and provided great

19 insight into how science impacts the real-life

20 experiences of people with pain, the great need for

21 a balanced approach to effectively manage pain, and

22 how it is individualized. She emphasized the

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1 importance of patients' active role in the process

2 and how patients need to be a part of their care

3 and management of pain.

4 Ms. Woods presented on the many current

5 applications and uses of MMEs in clinical practice,

6 regulations, dispensing, and reimbursement, as well

7 as in the research. It will be important to keep

8 these different applications in mind as we discuss

9 the science; that we need to better inform all

10 these varied applications of MMEs.

11 Dr. McPherson provided an overview of the

12 complexities of using MMEs for opioid conversion

13 and rotation in individual patients, starting with

14 the history of opioid conversion calculations,

15 problems with MME calculations, a newer paradigm

16 for calculating MMEs, as well as insight into

17 opioid use in the hospice population.

18 Dr. McPherson also presented on the wide

19 variation in results in the calculations of MMEs

20 amongst even healthcare providers, the varying

21 results from different online calculators, and

22 other differences, highlighting the variability

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1 that can directly impact patient care.

2 She encouraged much more nuanced thinking

3 about MME calculations and recommendations for

4 treatments based on experience and training that

5 one can get as a healthcare provider. This cannot

6 be an automated decision. It is much too complex

7 for that. Only one component of the decision

8 making may need a math app, and there is much more

9 complications, even with that, with the current

10 tables.

11 Dr. Fudin built upon and added a different

12 perspective to what Dr. McPherson discussed

13 regarding the need for individualization due to

14 differences in pharmacogenetics and varied

15 responses attributed to differing pharmacokinetics

16 and pharmacodynamics across patients.

17 Dr. Fudin also provided an overview of drug

18 characteristics such as differences in binding

19 affinity, partition coefficients, molecular

20 weights, and ultimately how these may inform a

21 range of equivalent equianalgesic doses.

22 The unique drug characteristics of methadone

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1 and fentanyl were presented, illustrating
2 drug-specific differences that create challenges
3 when calculating an MME. He also presented on how
4 pharmacists may be able to play a more active role
5 in opioid prescribing and informed considerations
6 of MME calculations and applications.

7 Next, our colleagues from the Veterans
8 Health Administration, Drs. Sandbrink, Emmendorfer,
9 and Cunningham, presented a wealth of information
10 on pain management and opioid safety in VA
11 patients. As shown in previous presentations, the
12 complexity of pain management and frequent
13 comorbidities of mental health conditions,
14 particularly for veterans, were highlighted. The
15 need for a multimodal, systemic coordination of
16 medical, psychological, and social aspects of
17 healthcare, an integrated approach, was presented.

18 Findings were shown that risk of suicide or
19 overdose exists at multiple doses of MMEs.
20 Patients with outcomes of overdose or suicide were
21 found to have total MMEs ranging lower than 90 MMEs
22 per day.

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1 Data on prescribing trends, urine tests, and
2 other measures were provided in regards to the VHA
3 Opioid Safety Initiative, as well as many other
4 risk mitigation strategies, including the need for
5 naloxone and close follow-up in how tapering should
6 be conducted very slowly.

7 The VA presentations provided insight into
8 their journey as a learning healthcare system for
9 pain management and opioid safety and highlighted
10 the importance of other patient-related factors,
11 other than MME, in predicting risk of overdose.

12 Next, we heard for from Dr. Kun Zhang on the
13 history and details of the Opioid NDC and MME
14 Analytical File compiled by CDC. Intended for
15 research and analytical purposes using claims or
16 dispensing data and surveillance of
17 population-level medical utilization, he emphasized
18 that the CDC file is not intended for clinical
19 decision making by prescribing physicians and has
20 been broadly misapplied.

21 Drs. Pittaway-Hay and Molinari presented
22 next on MHRA's similar journey in the UK on the

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1 development of MME tables with the goals of
2 improving information for opioid prescribers on the
3 safest possible effective dose of morphine or
4 equivalents.

5 In light of growing concerns about overuse
6 and misuse, an opioid expert working group was set
7 up in 2019 to review available evidence and
8 recommend ways to strengthen risk minimization
9 measures, improve communication, and educate
10 healthcare professionals and patients.

11 Their research centered around identifying
12 opioid conversion tables from regulatory and
13 institutional guidelines, online calculators, as
14 well as reviewing dose-reduction recommendations,
15 and recommended maximum MME thresholds from various
16 stakeholders.

17 Similar to findings discussed by
18 Drs. McPherson and Fudin, the working group
19 identified many limitations, including how there
20 were limited studies underlying the MME factors,
21 directional inequality, oversimplification of the
22 tables, and no clear threshold for a safe, maximum

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1 daily dose of MME.

2 As is the case in many other areas of
3 medicine, there is even less information and data
4 available for opioid therapy in the pediatric
5 population. Overall, there is a tremendous need
6 and desire for more information for prescribers and
7 other stakeholders in the complex treatment of
8 pain.

9 In our open public comment session, we heard
10 the voices and lives behind the numbers. We heard
11 individual accounts from patients with chronic and
12 sometimes intractable pain, and their families,
13 describing the impact that MME-based prescribing
14 and dispensing limits have had on their health care
15 and their quality of life.

16 Like Penney Cowan's remarks, these real-life
17 narratives remind us of the important -- I'm sorry.
18 Could you please mute your phone if you're not
19 speaking?

20 We also heard further calls to talk about
21 drug-specific concerns such as those associated
22 with calculating MMEs per day for buprenorphine,

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1 methadone, and tapentadol as further challenges in
2 need for creative solutions.
3 As mentioned earlier, we highly value the
4 public docket, and the public docket will be open
5 through August 9th for your feedback. You are
6 encouraged to post further comments, as we do
7 review them and value your voice.
8 That concludes my recap of day 1. On the
9 agenda today, we have six more presentations, and
10 to kick off presentations for today, we will now
11 hear more about opioid conversion information in
12 regards to FDA drug labeling from Dr. O'Donnell.
13 Thank you.
14 Presentation – Mary Therese O'Donnell
15 DR. O'DONNELL: Good morning, and welcome
16 back to day 2. My name is Therese O'Donnell, and
17 I'm a medical officer in the Division of
18 Anesthesiology, Addiction Medicine, and Pain
19 Medicine, and I will be discussing Opioid
20 Conversion Information in Approved Labeling.
21 First, I'll give some general background
22 about the amount and type of conversion information

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1 that is present in the labels relevant to the
2 immediate-release, extended-release, and long-
3 acting opioids. In addition, I'm going to go over
4 the specific details of some safety labeling
5 changes for opioid analgesics that provide
6 consistency and standardization of language in the
7 labels. And finally, I will go over the opioid
8 analgesic risk evaluation and mitigation
9 strategies, which FDA expanded in 2018 to cover all
10 opioid analgesics.
11 Opioids have been used for the treatment of
12 acute and chronic pain for the last several
13 decades. During the course of treatment, as
14 mentioned by multiple speakers yesterday, a subset
15 of patients may need to be switched from one opioid
16 or route of administration to another in a process
17 known as opioid rotation. This may occur because
18 the patient experiences intolerable side effects,
19 does not achieve adequate analgesia, or for several
20 other reasons.
21 The sections of the label that contain
22 relevant information on opioid conversion

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1 information include dosage and administration,
2 warnings and precautions, and the clinical studies
3 section.
4 To briefly summarize, the labels reviewed
5 contain general information and/or guidelines for
6 conversion from one opioid to another with
7 recommendations to underestimate the dose of the
8 new opioid due to interpatient variability,
9 possible incomplete cross-tolerance, and other
10 factors relative to the individual patient and
11 clinical setting.
12 In some of the extended-release labels,
13 specific conversion tables that were used in
14 clinical studies and submitted with the application
15 are also included in the label. I will go over
16 specific examples of these tables later. Finally,
17 the sources of opioid conversion information
18 referenced in the approved labeling include
19 published literature, consensus guidelines, and
20 specific clinical trial data.
21 I will now move on to review the
22 immediate-release opioid labels. These labels

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1 include general information on conversion from one
2 opioid to another and do not contain specific
3 information in the form of a conversion or
4 equianalgesic table.
5 This is the dosage and administration
6 section for immediate-release opioids. This
7 section provides recommendations for the initial
8 dosing, dose titration, and when appropriate, dose
9 tapering.
10 For the conversion from one opioid to
11 another, most immediate-release opioid labels have
12 general statements advising healthcare
13 professionals to refer to published relative
14 potency information, keeping in mind the conversion
15 ratios are only approximate. Due to significant
16 inter-patient variability in the potency of
17 opioids, it is also recommended to underestimate a
18 patient's initial 24-hour dosage rather than
19 overestimate.
20 The relative bioavailability of
21 immediate-release products compared to
22 extended-release opioids is unknown, so conversion

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1 to an extended-release opioid must be accompanied
2 by close observation for excessive sedation and
3 respiratory depression.
4 Moving on to extended-release, long-acting
5 opioids, all labeling includes general and, when
6 available, specific information on conversion in
7 the dosage and administration section. The
8 reference to interpatient variability of relative
9 potency is similar to the immediate-release product
10 label.
11 There are also two statements in warnings
12 and precautions relative to conversion that include
13 respiratory depression and death that may occur if
14 the dosage of a new opioid is overestimated when
15 converting from one product to another and the
16 avoidance of withdrawal when discontinuing opioids.
17 Extended-release opioids, as I mentioned,
18 with data from clinical trials to support specific
19 conversion factors may have those tables in
20 Section 2 of their label. The most important point
21 to note is that these conversion tables are
22 generally just that. They are not MME or

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1 equianalgesic tables, and the labels include
2 recommendations for dose modification based on the
3 individual product, and I will now go over such an
4 example.
5 This table was used as a guide in a clinical
6 trial of Hysingla ER that had an open-label
7 titration period during which subjects were
8 converted from their prior opioid to the
9 investigational product, Hysingla ER.
10 The conversion factors are specific only to
11 the listed oral opioids and can only be applied in
12 a unidirectional manner. They're only for use in
13 converting patients to the product in question and
14 are not to be used in the reverse direction, which
15 could lead to overdose.
16 In addition, the labels that have these
17 tables also include specific instructions on how to
18 calculate the initial dose. For Hysingla ER, the
19 first step is to use this table to convert the
20 prior oral opioid to a total hydrocodone daily
21 dose, and then to reduce the calculated daily
22 hydrocodone dose by 25 percent to account for

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1 interpatient variability in relative potency. Then
2 it recommends rounding down, if necessary, to get
3 the appropriate Hysingla- tablet strength,
4 maintaining close observation for signs of
5 withdrawal or oversedation on the new regimen.
6 The percentage reduction of the calculated
7 daily dose varies for each product. This is
8 another example of a conversion table, but it is
9 for pediatric patients 11 years and older. The
10 OxyContin label states that there are no
11 established conversion ratios for a conversion from
12 other opioids to OxyContin, defined by clinical
13 trial for adults. However, the label does have a
14 table for conversion of pediatric patients, based
15 on clinical trial experience.
16 Note that patients must be on and tolerating
17 opioids for at least 5 days, and also note the
18 qualification to adjust the conversion factor for
19 patients receiving high-dose parenteral morphine,
20 from 3 to 1.5.
21 I will now go over some of the changes that
22 have been implemented across opioid analgesic

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1 products to improve informed prescribing. In 2016,
2 FDA revised the package insert for all opioid
3 analgesics. This affected the immediate-release
4 products the most, as extended-release and long-
5 acting opioids went through a comprehensive
6 labeling change in 2013.
7 This included clear instructions regarding
8 the choices of the initial dose of an opioid
9 analgesic and dosage modifications when switching
10 from one opioid to another or when titrating the
11 dose. Later, the risk associated with abrupt
12 discontinuation was also added.
13 In 2018, the opioid analgesic REMS was
14 expanded to include all opioid analgesics used in
15 the outpatient setting. I will briefly review risk
16 evaluation and mitigation strategies.
17 REMS are intended for drugs with serious
18 risks that could outweigh the benefits, and they
19 can be required at the time of drug approval or
20 during the postmarket period if new safety
21 information becomes available.
22 REMS can be done in a variety of ways, and

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1 the elements can range from requiring special
2 training, to a patient registry, to allowing a drug
3 to only be dispensed in a certain setting. They
4 are designed to reinforce behavior either by the
5 healthcare provider, the patient, or both.

6 As of 2018, all extended-release, long-
7 acting, and immediate-release opioids intended for
8 outpatient use were required to participate in the
9 opioid analgesic REMS. The goal of this REMS is to
10 educate all healthcare providers, including
11 pharmacists and nurses, involved in the management
12 of patients with pain on the treatment and
13 monitoring of those patients.

14 The primary component is the FDA blueprint,
15 which contains a high level outline of the core
16 educational message. It includes the concepts and
17 limitations of the conversion charts in labeling
18 and the limitations of relative potency or
19 equianalgesic dosing in the literature.

20 The continuing education program is funded
21 by the pharmaceutical companies that are under this
22 opioid analgesic REMS. They do this by providing

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1 unrestricted grants to third-party accredited
2 continuing education providers, who then design and
3 make the training available for healthcare
4 providers.

5 In conclusion, not all immediate-release,
6 extend release, and long-acting opioid labels have
7 the exact same information on opioid conversion.
8 The content is specific to the data provided for
9 the individual product being approved. When
10 conversion factor tables are provided and are
11 supported by clinical data, they may be included in
12 the label.

13 All opioid labels do have information
14 regarding risks of initiating an opioid, making
15 dosing changes, converting from one opioid to
16 another, and in discontinuing products abruptly.

17 Thank you very much.

18 DR. CHAI: Thank you, Dr. O'Donnell. That
19 was really helpful to see and hear more about
20 opioid conversion information from the FDA's
21 perspective.

22 Next, we'll have a presentation from Dr. Dan

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1 Mellon and Dr. Donna Volpe, who will provide an
2 overview of Nonclinical Pharmacology and Toxicology
3 Considerations Regarding Opioid Comparisons and
4 Risks Assessments. I believe Dr. Mellon will be
5 presenting on behalf of Dr. Volpe as well.

6 Thank you, Dr. Mellon.

7 Presentation – Daniel Mellon

8 DR. MELLON: Good morning everyone, and
9 thank you for joining us on day 2 of this workshop.
10 My name is Dan Mellon, and today Dr. Volpe and I
11 have prepared this presentation to help set the
12 stage for further discussions of this very
13 challenging topic.

14 For the next 40 minutes or so, we are
15 actually going to take a step back from the clinic
16 and discuss some basic opioid pharmacology and
17 toxicology concepts to help shed light on the
18 potential role that pharmacology and nonclinical
19 toxicology can play when attempting to compare
20 opioids. First, we must note that as FDA
21 employees, you must be advised that this
22 presentation reflects the views of the authors and

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1 should not be construed to represent FDA policies
2 or views.

3 Our objectives for today include providing a
4 quick overview and history of opioid pharmacology,
5 get back to basics, if you will. We also want to
6 describe the challenges with attempting to compare
7 opioid potency from a basic science and nonclinical
8 perspective.

9 We will compare data from binding affinity
10 studies with toxicological endpoint data to
11 illustrate the challenge of potency estimates.
12 Finally, we hope to describe some of the challenges
13 that must be addressed when attempting to translate
14 animal potency data to humans.

15 As we all know, the origin of opioid
16 pharmacology is extremely old; in fact, no one
17 really knows how old it is. However,
18 archaeologists have found burial sites in Spain
19 dating back to 4200 BC that contains stashes of
20 poppy seed capsules, suggesting the plant had
21 significant meaning to these individuals over
22 6,000 years ago.

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1 The Sumerians knew of the potential of the
2 opioid poppy as well. In fact, as far back as
3 3400 BC, there is documentation that the Sumerians
4 referred to opium as "gil," which means joy, and
5 they referred to the poppy plant itself as
6 "hul gil" or plant of joy.

7 At this point, I want to provide a note on
8 terminology and distinguish the difference between
9 the words "opiate" and "opioid." They are often
10 used interchangeably but they are actually
11 different.

12 The term "opiate" is used to refer to
13 compounds derived from opium, the resin obtained
14 from the opioid poppy plant *Papaver somniferum*.
15 The term "opioid" is more inclusive and is used to
16 refer to all natural, semisynthetic, and synthetic
17 opioids such as fentanyl. So all opiates are
18 opioids, but not all opioids are opiates. I will
19 use the term "opioid" for the remainder of this
20 presentation.

21 Although we have known about poppy plants
22 and opium for thousands of years, it was not until

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1 sometime between 1803 and 1805 that morphine was
2 first extracted from opium resin by the German
3 pharmacist Friedrich Serturmer. In fact, morphine
4 was actually the first alkaloid ever extracted from
5 any plant.

6 The concept of an opioid receptor, however,
7 was first proposed in 1954 by Beckett and Casy
8 based on their evaluation of the rigid requirements
9 of chemical structures necessary for opioid
10 pharmacological activity. They postulated that
11 these requirements dictated the need for a set of
12 complementary structural requirements for receptor
13 binding sites in order to produce the effects of
14 opioids.

15 Although predicted in 1954, the actual
16 existence of opioid receptors was not demonstrated
17 until 1973 using radioligand binding assays by
18 three separate groups, Candace Pert and Solomon
19 Snyder; Eric Simon and his colleagues; and Lars
20 Terenius.

21 The term "ligand," which I will use
22 frequently in this presentation, is a

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1 pharmacological term that basically describes a
2 compound that binds to a biomolecule like a
3 receptor to produce a biological response. In
4 other words, for today's discussion, when I say
5 "ligand," you can think of this as an opioid drug.

6 To date, a total of four different opioid
7 receptors have been cloned, each coded by a single
8 gene. The receptors are all 7transmembrane
9 G-protein-coupled receptors. The three most
10 discussed in terms of studies of analgesia
11 historically have been the mu, delta, and kappa
12 opioid receptors.

13 The literature is filled with various terms
14 that have been used over the years to describe
15 these receptors, some of which are presented on the
16 slide in parentheses. For example, the mu opioid
17 receptor is commonly referred to by the Greek
18 letter μ . However, you will also see that it might
19 be represented as MOR for mu opioid receptor, MOP
20 for mu opioid peptide receptor, and even OP3 for
21 opioid peptide receptor 3.

22 Based purely on receptor binding studies and

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1 differential pharmacological profiles, there are
2 believed to be two subtypes of the delta receptor
3 called delta 1 and delta 2; three subtypes of the
4 kappa, kappa 1, kappa 2, and kappa 3; and three
5 subtypes of the mu opioid receptor, mu 1 mu 2 and
6 mu 3.

7 The fourth, opioid receptor, the nociceptin
8 orphanin FQ receptor, has been termed ORL-1 for
9 opioid receptor-like 1 protein. ORL-1 was cloned
10 based on sequence homology with the other opioid
11 receptors. This receptor is not sensitive to
12 naloxone, and to date less is known about it,
13 although it is actively being investigated for its
14 potential clinical utility as a target for
15 analgesia.

16 We will not further discuss ORL-1 today
17 because the currently approved opioid analgesic
18 drugs are not believed to have significant activity
19 at this receptor.

20 Like most G-protein-coupled receptors, the
21 mu, delta, and kappa opioid receptors are coupled
22 to pertussis toxin-sensitive G proteins. Upon

<p style="text-align: right;">Page 37</p> <p>1 activation and G-protein coupling, the receptor 2 results in multiple signal transduction events 3 mediated by the alpha and beta gamma subunits of 4 the G proteins. Intracellular signaling cascades 5 result in multiple downstream effects, including 6 inhibition of adenylyl cyclase, and thus decrease 7 cyclic AMP and protein kinase A activation. 8 In addition, binding of opioid antagonists 9 to opioid receptors result in reduced opening of 10 voltage-gated calcium channels, which results in 11 reduced neurotransmitter release from presynaptic 12 terminals. Third, activation of opioid receptors 13 results in stimulation of potassium currents 14 through several different channels, which results 15 in hyperpolarization of neurons. 16 Finally, data indicate that binding of 17 opioid antagonists to opioid receptors leads to 18 activation of protein kinase C and phospholipase C 19 beta. Also consistent with other G-protein-coupled 20 receptors, activation of opioid receptors can 21 result in the receptors being phosphorylated by 22 G-protein-coupled receptor kinases, or GRKs.</p>	<p style="text-align: right;">Page 39</p> <p>1 mediating this desensitization are complicated 2 given the diverse-signal transduction events that 3 occur after receptor binding. However, 4 phosphorylation of the receptor after activation is 5 believed to play a role. 6 After phosphorylation, the receptor may be 7 internalized via endocytosis, resensitized, and 8 recycled to the cell membrane or ultimately 9 degraded. Homologous desensitization refers to the 10 desensitization of the receptor following its own 11 activation. Heterologous desensitization, or 12 cross-desensitization, refers to desensitization of 13 other receptors on the cell following activation. 14 Both can occur and impact the overall activity of 15 the cell. 16 The term "drug tolerance" is more general. 17 This term refers to the loss of responsiveness to 18 an agonist after continued exposure without 19 specifying the cellular or molecular mechanism 20 mediating the loss of responsiveness. 21 We mentioned receptor internalization. This 22 is often referred to as receptor trafficking. What</p>
<p style="text-align: right;">Page 38</p> <p>1 Phosphorylation of the intracellular portion of the 2 receptor promotes interaction with the 3 intracellular protein beta arrestin, which 4 functions to turn off the G-protein mediated 5 signaling, helps target the receptor for 6 internalization, and redirect signaling to 7 G-protein independent pathways. 8 That leads us to the fact that opioid 9 receptors can desensitize, and ultimately 10 individuals can manifest drug tolerance. Let's 11 define those terms. 12 Desensitization usually refers to the 13 molecular changes at the level of receptor 14 signaling that result in progressive reduction of 15 signal transduction after receptor activation. For 16 opioid receptors, there is a rapid desensitization 17 that takes place in seconds to minutes. A short- 18 term tolerance can occur in minutes to tens of 19 minutes, and longer-term tolerance that can occur 20 after longer exposures to agonists, such as days. 21 This is illustrated in the figure on the 22 right side of this slide. The molecular mechanisms</p>	<p style="text-align: right;">Page 40</p> <p>1 is important to note is that data suggest that the 2 different opioid receptor subtypes respond to 3 ligand binding differently. 4 For example, both the mu opioid receptor and 5 the delta opioid receptor both undergo rapid 6 agonist-mediated internalization after receptor 7 activation. Data suggests that the mu opioid 8 receptor recycles to the membrane after 9 internalization. However, the delta opioid 10 receptor appears to be degraded after 11 internalization, and the kappa opioid receptor does 12 not appear to internalize at all. 13 The response of the receptor following 14 activation may actually differ depending upon the 15 ligand studied. For example, etorphine and 16 enkephalin binding to the mu opioid receptor 17 results in rapid internalization, whereas morphine 18 binding to the receptor does not appear to result 19 in significant receptor internalization. 20 This is illustrated in the table on the 21 right part of this slide. Both morphine and 22 etorphine result in G-protein activation, but the</p>

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1 mu opioid receptor is phosphorylated far more after
2 etorphine binding than morphine binding.
3 This results in greater beta-arrestin
4 recruitment and mu opioid receptor internalization
5 following etorphine compared to morphine. In
6 contrast, morphine binding to the mu opioid
7 receptor results in greater PKC activation and mu
8 opioid receptor desensitization than etorphine.
9 The take-home message, however, is that
10 different ligands may result in different
11 intracellular signal transduction cascade events
12 that can result in different receptor trafficking
13 responses, and thus different overall physiological
14 responses.
15 This also serves to introduce the concept of
16 a "biased ligand". As we noted earlier, opioid
17 receptor signal transduction involves both
18 activation of G-proteins and beta arrestins.
19 Activation of both of these trigger intracellular
20 signal transduction cascades.
21 Data suggest that beta arrestin not only is
22 involved in receptor phosphorylation and

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1 desensitization but can also result in other
2 intracellular signaling cascades that contribute to
3 the net effect of the opioid following binding to
4 the receptor. In fact, it has been reported that
5 activation of beta arrestin in G-proteins may
6 contribute to different physiological effects.
7 If true, then a specific opioid drug could
8 result in greater activation of G-proteins compared
9 to beta-arrestin pathways, which has been proposed
10 to be associated with greater analgesic effects and
11 less adverse side effects, while a different opioid
12 drug that results in greater beta-arrestin
13 activation than G-protein activation could result
14 in greater adverse side effects and less analgesia.
15 Drugs that result in this unbalanced
16 activation are referred to as biased ligands. The
17 different intracellular signaling effects of
18 various opioids may alter the ultimate
19 physiological response, possibly contributing to
20 differential efficacy, adverse effects, and rates
21 of desensitization.
22 This is illustrated in the figure borrowed

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1 from Dr. Williams and colleagues' excellent review
2 in Pharmacological Reviews. The X-axis represents
3 the bias factor. A value above zero indicates a
4 bias toward G-protein activation and a value below
5 zero indicates a bias toward beta-arrestin
6 activation.
7 DAMGO is an experimental peptide highly
8 selective for the mu opioid receptor and shows a
9 bias toward G-proteins, depicted in the red bar and
10 number 1 in the figure. Morphine is depicted in
11 the dark blue and the number 5 on this plot, and
12 shows little bias.
13 Oxycodone, depicted as number 6 and orange
14 bar, is similar to morphine. Norbuprenorphine, an
15 active metabolite of buprenorphine, and alfentanil,
16 depicted here in green and a slightly darker blue,
17 or numbers 12 and 13, respectively, show a bias
18 toward beta-arrestin activation.
19 Although it is not yet clear if these
20 differences are clinically significant, the point
21 is that not all opioids produce the same downstream
22 signal transduction events.

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1 To add to the complexity, we cannot ignore
2 the impact of genetics on basic pharmacology. Not
3 only do genetics impact how drugs like opioids are
4 metabolized, but there are data that suggests that
5 a person's genetic makeup may well impact how they
6 respond to opioid analgesics.
7 For example, there is a single nucleotide
8 polymorphism termed RS1799971 that results in a
9 change in a single nucleotide from adenine to
10 guanine in a gene that codes for the mu opioid
11 receptor called OPRM1. This single nucleotide
12 polymorphism is present in 15 to 30 percent of
13 Europeans, 40 to 50 percent of Asians, but only
14 1 to 3 percent of people of Latin or African
15 American descent.
16 That single nucleotide change results in a
17 change in the amino acid at position 40 from
18 asparagine to aspartate. That's not necessarily
19 inconsequential because that change removes an
20 amino acid that can be glycosylated.
21 Glycosylation of that asparagine can impact
22 mu opioid ligand binding, signal transduction, and

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1 even the half-life of the receptor. In addition,
2 the single nucleotide change adds a possible
3 methylation site that can lead to reduced mu opioid
4 receptor mRNA.

5 Speaking of methylation sites, there are
6 epigenetic changes that can occur via methylation
7 of the OPRM1 promoter that have been linked to
8 various physiological conditions such as alcohol
9 dependence, opioid dependence, pain responses,
10 neuropathic pain conditions, and even Alzheimer's
11 disease.

12 Finally, splice variants of the mu opioid
13 receptor exist. For example, in contrast to the
14 7-transmembrane receptor, there is a splice variant
15 that results in a 6transmembrane receptor that has
16 been noted to result in differential effects on
17 efficacy and adverse-effect profiles.

18 Predicting how binding of an opioid drug to
19 its receptor can impact its overall effect is even
20 more challenging because data suggests that opioid
21 receptors can dimerize. So not only can we have
22 mu, delta, or kappa receptors, but there is

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1 evidence that mu-mu dimers can form, delta-delta
2 dimers, or kappa-kappa dimers.

3 Dimerization of receptors can impact ligand
4 binding, intracellular signaling, and receptor
5 trafficking and desensitization. Even more
6 challenging, hetero dimers can occur such that a
7 mu opioid receptor could dimerize with a kappa
8 opioid receptor. Likewise, a delta opioid receptor
9 could dimerize with a kappa receptor, and a
10 mu opioid receptor could dimerize with a delta
11 opioid receptor.

12 Finally, opioid receptors have also been
13 reported to dimerize with other non-opioid
14 G-protein-coupled receptors, leading to an even more
15 complicated impact on downstream cellular effects
16 and ultimately pharmacodynamic effects.

17 That leads us to the pharmacodynamic effects
18 of opioids believed to be mediated by these various
19 opioid receptors. We all know that activation of
20 mu opioid receptors is strongly linked to
21 analgesia, physical dependence, euphoria, miosis,
22 reduced gastrointestinal motility, and of course

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1 respiratory depression. Those effects are well
2 known for mu opioid ligands.

3 There is less known, however, about the
4 clinical significance of ligands that bind to the
5 delta and kappa receptors, but data suggest that
6 delta receptor binding may also contribute to
7 analgesic responses. But they've also been
8 associated with antidepressant effects,
9 proconvulsant effects, physical dependence, and
10 even modulation of mu opioid receptor-mediated
11 respiratory depression.

12 Activation of the kappa receptor has also
13 been linked to analgesia, as well as anticonvulsant
14 effects, depression, dissociative effects,
15 hallucinations, neuroprotection, and even stress.

16 Drugs which act at multiple opioid receptors,
17 sometimes referred to as mixed-opioid
18 agonists/antagonists, may have slightly different
19 effect profiles.

20 In fact, data indicate that not all
21 clinically-used opioid analgesics have the same
22 opioid receptor binding profile. Morphine and

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1 hydromorphone are predominantly mu opioid agonists
2 but do have some kappa agonist activity. Fentanyl
3 and methadone, on the other hand, seem to be more
4 selective for the mu opioid receptor with little,
5 if any, kappa activity.

6 Buprenorphine, as we have heard, is a
7 partial agonist at the mu opioid receptor and
8 antagonist at the kappa opioid receptor. We'll
9 discuss that term "partial agonist" a bit more in a
10 minute. Interestingly, the metabolite
11 norbuprenorphine appears to have full agonist
12 activity at the mu opioid receptor.

13 Finally, butorphanol appears to be a partial
14 agonist at the mu opioid receptor and a full
15 agonist at the kappa opioid receptor. Different
16 binding profiles to the various opioid receptors
17 likely contribute to subtle differences and effects
18 in humans.

19 Let's step back and refresh our memories of
20 how we measure opioid receptor binding so that we
21 can better compare what we know about
22 clinically-used opioid analgesics.

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1 Receptor binding studies measure the
2 affinity of a ligand for the receptor. These
3 studies historically have used a radiolabeled
4 ligand, such as tritiated naltrexone or DAMGO, that
5 binds to the receptors in a tissue or membrane
6 sample and eventually saturate the receptors in the
7 preparation.

8 This is depicted in the figure to the right.
9 Percent bound is on the Y-axis and the
10 concentration of the drug is on the X-axis. The
11 red line shows a binding of a relatively high
12 affinity ligand to the receptor such that it
13 reaches 100 percent at relatively low
14 concentrations. In contrast, a lower affinity
15 ligand may require higher concentrations to occupy
16 100 percent of the receptor binding sites, as shown
17 here in green.

18 To compare the binding affinity of
19 compounds, we can actually do the study in one of
20 two ways. We can measure a direct binding affinity
21 by radiolabeling the compound of interest and
22 testing the saturation as we just described.

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1 Alternatively, we can do an indirect binding assay
2 by saturating all receptors with a radiolabeled
3 compound like tritiated DAMGO and test increasing
4 concentrations of the unlabeled drug of interest to
5 see how well we can displace the radiolabeled
6 compound from the receptor.

7 To compare affinity, we compare the
8 concentration at which 50 percent of the receptors
9 are occupied by the radioligand. In a direct
10 binding assay, affinity is defined by the K_d or
11 dissociation constant. The K_d is the concentration
12 at which 50 percent of the receptors are occupied.
13 The smaller the K_d , the higher the affinity of the
14 drug for the receptor.

15 In an indirect binding assay, we define
16 affinity as the K_i or inhibition constant. The K_i
17 is the concentration at which 50 percent of the
18 radioligand is displaced from the receptor. The
19 smaller the K_i , the higher the affinity. This gives
20 us a way to compare receptor binding affinities for
21 various compounds like opioid analgesics.
22 Binding affinity measures how well a

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1 compound binds to a receptor. It does not indicate
2 if the binding to the receptor activates signal
3 transduction like an agonist or blocks signal
4 transduction like an antagonist. This plot
5 illustrates the types of functional responses that
6 can occur after a compound binds to a receptor
7 compared to the receptor binding data.

8 First, let me draw your attention to the red
9 dashed line. This line depicts receptor binding
10 saturation like the plots we just looked at. You
11 can consider that Y . As you increase concentration
12 of a drug, the drug occupies more and more
13 receptors but eventually saturates the receptors.

14 The types of agonist binding functional
15 responses which can occur can be described by
16 comparing the functional physiological response or
17 activity that results from binding to the receptor
18 saturation state. In this figure, the Y-axis is
19 labeled the activity fraction divided by Y . Think
20 of the activity fraction as a measured effect of a
21 drug such as activation of G-proteins in a cell or
22 even analgesia. If you divide the functional

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1 pharmacodynamic response by the receptor occupancy,
2 a value of 1 represents maximal receptor occupancy
3 and a maximal physiological response.

4 Let's look at the blue Line. A full agonist
5 like DAMGO is able to produce a maximum functional
6 response when receptors are fully occupied. In
7 contrast, let's look at the green line in the
8 figure. If a compound saturates the receptors but
9 does not result in a maximum physiological response
10 such as depicted by the green line in this figure,
11 it is referred to as a partial agonist, meaning it
12 can only result in part of the full response
13 compared to the full agonist.

14 The orange line depicts an antagonist. An
15 antagonist binds to the receptor and can completely
16 saturate the binding sites, but binding does not
17 result in any physiological response. The purple
18 line depicts an inverse agonist, which we will not
19 discuss further today after this slide. An inverse
20 agonist binds to the receptor and actually results
21 in a reduction of the activity being measured. For
22 example, instead of decreasing intracellular cyclic

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1 AMP levels like opioids do, the drug actually
2 increases intracellular cyclic AMP levels upon
3 receptor saturation.
4 This categorization of drugs is useful to
5 help compare opioids which show diverse responses.
6 In fact, in experimental opioid pharmacology, DAMGO
7 is considered the full agonist, and many
8 FDA-approved drugs do not produce the same
9 magnitude of effect as DAMGO in various
10 experimental conditions, indicating that this may
11 not be an all-or-nothing phenomena, and drugs show
12 varying degrees of full agonist activity.
13 Several years ago, FDA conducted studies to
14 compare binding affinities of clinically-used
15 opioid analgesics as a surrogate for opioid
16 potency. The challenge at the time was to obtain
17 data to help delineate what opioid drugs were more
18 dangerous than others in order to have data to
19 inform opioid drug product disposal recommendations
20 in labeling; for example, recommendations of
21 flushing unused drugs down the toilet rather than
22 other means of disposal that could result in

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1 increased risk for diversion or inadvertent
2 exposure to household members or pets.
3 As part of that process, Dr. Volpe and her
4 team reviewed the existing published literature to
5 see what data were already available to compare
6 opioid receptor affinities with the focus on a
7 mu opioid receptor because activation of the
8 mu opioid receptor is known to result in
9 respiratory depression.
10 The review of the literature concluded that
11 there is a wide range of binding affinities
12 reported for opioid compounds at the mu opioid
13 receptor. This is likely due to differences in
14 methodology; for example, the radioligands used,
15 the compounds used to define nonspecific binding,
16 the laboratory methods employed, the tissues
17 evaluated, the species tested, just to name a few.
18 This figure depicts the range of K values
19 reported in the literature for binding affinity
20 measurements of ligands at the mu opioid receptor.
21 The Y-axis lists the clinical opioid analgesic and
22 the X-axis list the K value, or indirect binding

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1 constant, in nanomolar concentrations.
2 I must point out that this is a log scale.
3 Morphine binding is depicted in the darker green
4 color and range from less than 1 nanomolar to
5 almost a thousand nanomolar. Fentanyl, in red,
6 ranges from 0.01 nanomolar to approximately
7 200 nanomolar.
8 There are some expected trends from these
9 data. For example, a compound like sufentanil, in
10 burgundy at the top-left of the figure, generally
11 shows lower K values, meaning higher affinity, than
12 a compound like codeine, the black bar near the
13 bottom-right of the figure. However, given the
14 variability in these reported binding affinities,
15 use of these data for direct comparisons was not
16 considered ideal.
17 Similar ranges for binding affinities of
18 these compounds were also reported for delta and
19 kappa binding sites as illustrated in these two
20 figures. Clearly, relying on the diversity of data
21 in the published literature was not going to be
22 ideal to compare FDA-approved opioid drugs given

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1 the variability in the results that reported.
2 Therefore, Dr. Volpe and her team attempted
3 to eliminate as many confounding variables as
4 possible to generate a single set of data for
5 FDA-approved analgesics in order to obtain a
6 uniform assessment for ranking of mu opioid
7 receptor binding affinities. To do this, they
8 employed an indirect receptor binding assay, as we
9 described just a few moments ago, to determine the
10 affinity of FDA-approved opioid analgesics.
11 Specifically, these binding data generated
12 K values using radiolabeled DAMGO displacement from
13 commercially available tissue preparations,
14 expressing recombinant human mu opioid receptors.
15 This approach standardizes the tissues and
16 receptors being studied, the radioligand employed,
17 the definition of specific binding for the assay,
18 the laboratory methods, and even the scientists who
19 completed the actual assays.
20 The result was some of the prettiest
21 receptor binding plots I've ever seen, and I take
22 no credit for these. The indirect binding

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1 displacement plots are on the left, showing
2 displacement of tritiated DAMGO from the receptors
3 for each compound. The K values in nanomolar are
4 in the table on the right, ranked from highest
5 affinity to lowest. Remember, a low K means a high
6 affinity of the compound for the receptor. The red
7 box depicts the K for morphine, which in this
8 system was one 1.168 nanomolar.
9 Many of these affinities are consistent with
10 what we would expect. For example, sufentanil,
11 hydromorphone, and oxymorphone have higher affinity
12 for the mu opioid receptor than morphine and are
13 believed to be more potent. Likewise, codeine and
14 tramadol have lower affinities than morphine and
15 are known to be less potent than morphine.
16 As we heard yesterday from Dr. Fudin,
17 codeine is metabolized to morphine, so we do have
18 to take that into consideration when comparing
19 potency. Tramadol has a very low affinity, but
20 that actually makes sense as well because we know
21 that tramadol itself does not really bind to opioid
22 receptors; rather it is the M1 metabolite of

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1 tramadol that binds to the mu opioid receptor.
2 But let's look at these data a bit closer.
3 The slide is small, granted, but fentanyl, which we
4 know is commonly considered to be about 100 times
5 more potent than morphine as an analgesic, has a
6 binding affinity which is actually slightly lower
7 than that of morphine, a slightly higher K.
8 Likewise, oxycodone, commonly considered to be
9 about 1 to 2 times more potent than morphine,
10 actually has a binding affinity that is 22 times
11 less than morphine.
12 Yesterday, we heard from Dr. McPherson that
13 the difference may be, in part, due to very
14 different oral bioavailability for oxycodone
15 compared to morphine. Clearly, binding affinity
16 alone does not predict potency in all cases, but
17 understanding how a drug binds to the receptors is
18 an important piece of information to consider when
19 considering opioid comparisons.
20 Unfortunately, we don't have comparable data
21 for uniform binding affinities for these opioid
22 analgesics to kappa or delta opioid receptors, as

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1 that was not the aim of the study at the time.
2 Now let's explore these data a bit further
3 by looking at other factors that may contribute to
4 opioid potency. In this table, we present the
5 mu opioid binding affinity data we just looked at
6 and compared, as available, to reported rat oral
7 LD values. LD stands for the dose that is lethal
8 in 50 percent of the animals.
9 We don't generate these data anymore, as
10 these studies require a large number of animals in
11 order to be accurate, although comparing these
12 values does provide a relative understanding of the
13 lethal overdose potential of various drugs.
14 As we expected, fentanyl is very potent in
15 terms of potential lethality. It has an LD of
16 18 milligram per kilogram in the rat. In contrast,
17 the LD for morphine in this model was 461 mg/kg;
18 that is, it takes about 25 times a higher dose of
19 morphine to result in 50 percent mortality compared
20 to fentanyl.
21 The potency of fentanyl, as we heard in
22 Dr. Fudin's presentation yesterday, can in part be

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1 explained by its lipophilicity. Drugs that have a
2 high lipophilicity partition into fat, and
3 therefore can cross the blood-brain barrier
4 quickly. We can measure lipophilicity by comparing
5 how well a compound partitions in something that
6 analogous to fat like octanol versus water.
7 In the table, I have listed the
8 octanol-water partition coefficient. We can see
9 that fentanyl partitions into octanol quite well
10 compared to water, 860 compared to 1. In contrast,
11 the octanol-water partition coefficient for
12 morphine is 1.42 to 1, which makes it far less
13 lipophilic. Lipophilicity clearly contributes to
14 potency in vivo.
15 Now let's look at buprenorphine. We know
16 that buprenorphine is a partial agonist at the
17 mu opioid receptor. Receptor binding affinity is
18 actually about 5 times higher -- 5 times smaller
19 K value, compared to that of morphine. In other
20 words, it takes about 5 times lower concentration
21 of buprenorphine to occupy half the receptors
22 compared to morphine. However, because it is a

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1 partial agonist and does not result in maximal
2 activity, even when 100 percent of the receptors
3 are occupied, the oral rat LD is estimated at
4 50
5 greater than a thousand milligram per kilogram.
6 The take-home message here is that binding
7 affinity alone, although one important way we can
8 compare opioids, does not completely dictate
9 potency, and many factors have to be considered
10 when comparing opioids.
11 There are many experimental ways to measure
12 potency. For example, there are in vitro assays
13 such as the receptor binding studies we just
14 examined or in vitro studies to measure G-protein,
15 activation, inhibition of adenylyl cyclase, calcium
16 influx, or cyclic AMP inhibition. Each of these
17 assays contribute to our understanding of the
18 cellular responses following opioid receptor-ligand
19 binding.
20 There are also in vivo studies that can be
21 used to compare opioids. For example, we can
22 measure pain responses in animals by studies such
23 as the tail-flick assay, or study responses to

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1 painful stimuli in knockout animals; for example,
2 animals that lack specific receptors or express
3 differential receptor variants.
4 However, the challenge with any of these
5 assays is the same faced by Dr. Volpe and the FDA
6 team. We do not have uniform data for
7 clinically-relevant opioids in each of these
8 endpoints.
9 Let's discuss more of the challenge of
10 extrapolating animal pain responses to humans. In
11 humans, we measure analgesia, which is defined by
12 Merriam-Webster as "insensitivity to pain without
13 loss of consciousness." This is commonly assessed
14 by asking the person how much pain they feel using
15 a variety of scales such as a visual analog scale;
16 for example, rate your pain from 0 to 10, with 0
17 being no pain and 10 being the worst pain you've
18 ever felt or unbearable pain.
19 We know that there is both a sensory and an
20 emotional component to analgesia in humans. For
21 example, opioids not only alter signaling of pain
22 from a banged shin to the brain via the pain

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1 pathways, they can also impact our emotional
2 response to that pain that we do feel. We can also
3 measure children's perception of pain using a scale
4 with images to help depict how they feel such as
5 the faces scale depicted here.
6 We heard yesterday that assessing pain
7 responses and analgesia in humans is not simple,
8 but it's even harder in animals. As we know, we
9 cannot discuss with animals how much pain they
10 feel, and we have no idea about their emotional
11 response to a painful stimulus. As such, we don't
12 use the term analgesia in nonclinical research; we
13 use the term anti-nociception. Anti-nociception,
14 according to Merriam Webster, is "the action or
15 process of blocking the detection of a painful or
16 injurious stimulus by sensory neurons."
17 One early method used to measure
18 anti-nociception is the tail-flick assay. In this
19 assay, you must first acclimate a rodent to the
20 testing process and apparatus to minimize the
21 impact of stress on the animal. Once the tail is
22 comfortably lined in a small groove on the surface

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1 of the device, you shine a radiant heat source,
2 basically a light beam, on the tail and measure the
3 amount of time it takes for the rodent to flick the
4 tail away from the light.
5 The assay conditions are such that the heat
6 source does not injure the tail; only makes it
7 uncomfortable enough to result in the animal
8 flicking it away from the heat source. If a drug
9 produces anti-nociception, the rat will not flick
10 the tail as fast, if at all.
11 Please note that the study conditions are
12 established such that if the animal does not
13 respond by flicking the tail away, which can occur
14 with opioids, the heat source times out to prevent
15 tissue injury and inflammation.
16 The tail-flick assay has been around since
17 about 1941. This image from Dr. Gonzalez-Cano and
18 colleagues' excellent review describes the
19 evolution of the various assays that have been
20 investigated to try to measure nociception in
21 animals.
22 As you can see from the figure, more recent

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1 models are trying to include emotional responses to
2 painful stimuli in the animals by including
3 endpoints of behaviors thought to signify stress
4 and anxiety, including burrowing behavior or
5 nesting, and even more recent attempts to evaluate
6 facial expressions in the animals.
7 The important point here is that there are
8 many ways to assess the response to stimuli in
9 nonclinical models, but they are models and may or
10 may not entirely predict potency of analgesics in
11 humans. Nonetheless, they are extremely useful for
12 drug discovery and could be employed to generate a
13 uniform assessment of FDA-approved opioid analgesic
14 potency and contribute to the body of knowledge we
15 currently have.
16 Unfortunately, we are not aware of a
17 comprehensive uniform assessment of FDA-approved
18 opioid analgesics in any of these models, and
19 significant variability can occur between
20 laboratories and methods used to make cross-study
21 comparisons challenging.
22 To conclude, there are certainly both

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1 strengths and limitations of nonclinical assays.
2 In vitro studies have utility in that they can
3 focus in on one or a few endpoints relevant to
4 opioid pharmacology and opioid receptor potency
5 comparisons such as measurements of opioid receptor
6 binding or intracellular signal transduction
7 events. However, there is inter-laboratory
8 variability and generally a lack of uniform
9 assessments for all FDA-approved opioids in any
10 single model.
11 In vivo nonclinical studies can also provide
12 useful information to compare opioids, however,
13 there are species and even strain differences,
14 receptor density differences, and possibly
15 differences in metabolism and transport in animals
16 compared to humans.
17 Although nonclinical data are useful to
18 inform the basic science of opioid pharmacology,
19 there are clearly translational challenges with
20 nonclinical studies, such as attempting to predict
21 analgesia in humans by measuring anti-nociception
22 in a highly controlled animal model.

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1 The question we all face is, is it possible
2 to develop an ideal algorithm to account for all
3 variables that contribute to analgesia and adverse
4 event profiles for a given individual in order to
5 compare opioids? Possibly, but the data clearly
6 indicates that there are both drug and drug product
7 factors that should be accounted for, as well as
8 individual patient factors, as we have heard about
9 in prior talks.
10 For example, drug and drug product specific
11 factors include the selectivity of the drug for
12 various opioid and non-opioid receptor in the pain
13 pathways and the impact of genetics on receptor
14 expression and receptor splice variants that can
15 contribute to variability in responses.
16 The dosage form and the route of
17 administration clearly impact efficacy and safety,
18 the relative bioavailability of different compounds
19 and dosage formulations, the affinity and avidity
20 of the drug for the targeted receptors, the rate of
21 desensitization, and even protein binding
22 characteristics all contribute to variability for

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1 any given individual.
2 As we have heard in earlier talks, there are
3 also individual patient factors that would also
4 have to be accounted for, including age, sex, body
5 mass, kidney and liver function, degree of existing
6 tolerance, concomitant medications, and supplement
7 use. Underlying disorders and of course genetic
8 differences in receptors, enzymes, and transporters
9 can all result in differential patient responses.
10 I will end with some final thoughts. As we
11 all know, opioid pharmacology is incredibly old,
12 and yet there's still a great deal unknown. Basic
13 science and nonclinical studies can certainly
14 contribute to the foundation of knowledge we need
15 to help understand the variables necessary to be
16 able to compare opioid potencies for a given
17 individual.
18 However, cross-study comparisons of in vitro
19 and in vivo nonclinical data in the published
20 literature are extremely challenging, given the
21 variabilities that exist and methods employed; and
22 in theory, uniform assessments may help standardize

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1 values that could be considered in an algorithm.
2 Obviously, we cannot just look at one endpoint to
3 predict cross-opioid comparisons. We need to
4 consider the relative contribution of the many
5 variables that can impact outcome in order to
6 ultimately develop an ideal algorithm.
7 Finally, it is worth noting that nonclinical
8 studies can inform on specific differences between
9 opioids in a highly controlled setting, but the
10 results require integration into the entire body of
11 knowledge and ultimately testing in the clinical
12 setting, given the variabilities present in humans.
13 On behalf of Dr. Volpe and myself, we want
14 to thank you for your attention today, and we hope
15 that you are finding the workshop both informative
16 and useful.
17 DR. CHAI: Thank you, Dr. Mellon and
18 Dr. Volpe. That was fantastic. I know you're
19 calling it basic opioid pharmacology 101, but you
20 just broke down such complex topics in a way that
21 was digestible for us, and just really appreciate
22 the overview that you did. I'm sure that it's

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1 going to really help in our discussions, especially
2 as we tackle questions like question number 2 in
3 our panel discussions, so we look forward to that
4 time later today.
5 Now, we'll hear from Dr. Chad Reissig, who
6 will provide an overview of abuse liability
7 considerations from an FDA perspective.
8 Thank you, Dr. Reissig.
9 Presentation – Chad Reissig
10 DR. REISSIG: Great. Thank you so much.
11 Today I want to talk about MME Calculations
12 and Abuse Liability Considerations. I'll give you
13 a quick overview of today's talk.
14 I'll begin by talking about what is
15 addiction, how do we measure and define it, and
16 then I'll move to discussion about addiction in a
17 regulatory context. This is where I'm going to
18 spend the majority of the time of my talk, where
19 I'll be talking about abuse liability assessment,
20 focusing on two main areas.
21 These are the preclinical methodologies that
22 we use, more specifically, self-administration

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1 studies in rodents, and I will also discuss
2 clinical abuse liability assessments, the studies
3 that we do in humans. What we want to talk about
4 is whether or not there is a role for abuse
5 liability assessments in MMEs.
6 What is addiction? It's a complex
7 behavioral syndrome that's defined in a number of
8 ways. For example, the National Institute on Drug
9 Abuse says that, "Addiction is defined as a chronic
10 relapsing brain disease that is characterized by
11 compulsive drug seeking and use, despite harmful
12 consequences."
13 The Substance Abuse and Mental Health
14 Services Administration, or SAMHSA, says that,
15 "Substance use disorders occur when the recurrent
16 use of alcohol and/or drugs cause clinically
17 significant impairment, including health problems,
18 disability, and failure to meet major
19 responsibilities at work, school, or home."
20 Drug abuse can be defined as the intentional
21 non-therapeutic use of a drug product or substance,
22 even once, to achieve a desired psychological or

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1 physiological effect, and repeated incidence of
2 drug abuse may in fact lead to addiction.
3 So how do we measure addiction? Well,
4 unfortunately, there are no biomarkers or
5 laboratory-based assessments that are able to
6 diagnose or measure addiction. I can't draw a
7 patient's blood or scan their brain to come up with
8 an objective indicator of addiction. And in fact,
9 clinical diagnosis and outcome measures of
10 addiction are usually qualitative in nature. For
11 example, they include things like the Diagnostic
12 and Statistical Manual of Mental Disorders, which
13 is now in its 5th edition, DSM-V, and diagnoses in
14 the International Classification of Diseases, or
15 ICD.
16 So, for today's discussion about addiction
17 abuse liability and MMEs, morphine milligram
18 equivalent calculations, they do not currently take
19 abuse liability considerations into account and, in
20 fact, this is appropriate due to the complexity of
21 including abuse liability as part of the composite
22 MME calculation and also difficulties in defining

<p style="text-align: right;">Page 73</p> <p>1 addiction and abuse potential as a discrete 2 phenomena. 3 However, we do have a variety of scientific 4 methodologies that we utilize to both evaluate and 5 predict the abuse potential of drugs, and FDA 6 actually has a guidance on this. As described in 7 our final guidance, the Assessment of Abuse 8 Potential of Drugs, A Guidance for Industry, we use 9 a variety of data to evaluate abuse potential, 10 including chemistry information. 11 If a new drug is under review, we'll take a 12 look at the basic structure of the drug and see if 13 it resembles a known drug abuse. Receptor-ligand 14 binding studies that Dr. Mellon just talked about 15 are also used, along with functional studies like 16 indices of the activation of second-messenger 17 pathways. 18 Pharmacokinetic studies can be used in abuse 19 liability assessments and abuse related studies in 20 animals. These typically include things like 21 general behavioral observations, what happens when 22 an animal is administered a particular drug; drug</p>	<p style="text-align: right;">Page 75</p> <p>1 abusing a particular test compound during the 2 developmental stage. 3 Of those studies, the ones that I want to 4 talk to you today about are assays that directly 5 assess the reinforcing effects of drugs because 6 these may be the most relevant to MME calculations. 7 The two that I'd like to talk about are 8 abuse-related studies in animals or the classic 9 self-administration study, and also I want to take 10 some time to talk about the human abuse potential 11 study, the HAP study. 12 Starting with self-administration, this is 13 often considered the nonclinical gold standard of 14 abuse liability assessment. When you use this 15 technique, a laboratory animal has the opportunity 16 to either obtain or self-administer a drug. If the 17 drug is self-administered, we can track how often 18 and how much. 19 Here's a cartoon depicting the basic setup 20 of a self-administration study. What you see here 21 is a classic operant chamber, and on the right-hand 22 side of the chamber there are two levers along with</p>
<p style="text-align: right;">Page 74</p> <p>1 discrimination studies; self-administration 2 studies; and also physical dependence studies in 3 animals. 4 Abuse-related studies in humans are also 5 used, and this includes the human abuse potential 6 study, or the HAP, which is our gold standard of 7 abuse liability assessment, and also physical 8 dependence studies that are able to give us an idea 9 of withdrawal-related effects that may occur if a 10 patient stops taking a drug. 11 Abuse-related adverse events from clinical 12 studies are also used, and we can look at an AE 13 profile across all phases of development to see if 14 we see things like incidence of euphoria and other 15 measures. 16 Information related to overdose during 17 clinical studies has been utilized in the review of 18 new drugs, and we can see from the case report 19 forms what happens to patients and the 20 circumstances surrounding these. And finally, 21 assessment of the incidence of abuse during 22 clinical studies; on occasion, subjects may begin</p>	<p style="text-align: right;">Page 76</p> <p>1 a cue light. That cue light is illuminated to 2 indicate to the animal that the session is in fact 3 active, that they can press the lever, and then 4 response will occur. 5 Typically, the animals undergo a surgical 6 procedure in which an infusion pump is surgically 7 implanted into the back of the animal, and through 8 this pump we can then self-administer drug when the 9 animal presses the correct lever. 10 These are the data that we get from 11 self-administration. What I'm showing you here is 12 an unknown or new drug with suspected abuse 13 potential, and you are looking at the type of data 14 that would be generated if, in fact, the drug was 15 reinforcing. What I'm showing here is the classic 16 inverted U-shaped self-administration curve. You 17 get this curve in self-administration studies when 18 we examine a variety of known drugs of abuse. 19 I'll take a minute to orient you to the axes 20 here. On the X-axis, we have the unit dose of 21 drug, and on the Y-axis, we have the number of drug 22 injections per hour, although it could be along a</p>

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1 variable time schedule such as 2 hours, 4 hours, or
2 even a 24-hour self-administration procedure.
3 All the way to the left, you see a placebo
4 condition, and you see that when an animal receives
5 saline or placebo, it typically does not
6 self-administer very much, and likewise, as we move
7 from left to right, low doses of a drug of abuse
8 typically do not engender a lot of self-
9 administration.
10 As we increase the dose, we see that the
11 animal begins to self-administer drug, reaching a
12 peak in the middle of the graph. Now something
13 interesting happens if the dose continues to
14 increase, and that is that the self-administration
15 actually decreases.
16 Now, the reasons for this aren't entirely
17 known, but we think it may happen for a number of
18 reasons. One is satiation. The dose is high
19 enough. The animal had enough. He doesn't need to
20 self-administer very much of the drug because the
21 dose is so high.
22 Sometimes a drug may produce direct

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1 impairment, which also can decrease the
2 self-administration of the drug. A good example of
3 this would be with a sedative type drug, where if
4 the dose is high enough, an animal may self-
5 administer it once and go to sleep for the rest of
6 the session. And finally, at higher doses, a drug
7 may actually become aversive, so that may also
8 account for a decrease in self-administration as
9 the dose decreases.
10 Self-administration studies in animals, they
11 offer information about the range of doses of a
12 drug that are reinforcing, but they are limited in
13 determining relative reinforcement effects of
14 drugs; for example, whether one drug has increased
15 reinforcing effects compared to another.
16 One reason this is, is because of that
17 inverted U-shaped curve that I just showed you.
18 Oftentimes, we may not know where along that curve
19 we lie, so we may not know whether we're on the
20 ascending or the descending side, so it's rather
21 hard to make direct comparisons using basic
22 self-administration procedures.

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1 Because of that, generally, human abuse
2 liability assessments are considered face valid and
3 highly relevant indication of abuse liabilities.
4 If human abuse potential studies and nonclinical
5 studies do not show the presence of rewarding
6 effects or abuse-related behaviors, then we think
7 that widespread abuse of the drug is in fact
8 unlikely.
9 How do we do these human abuse potential or
10 HAP studies? Well, we begin in the same way that
11 we do any clinical study, by recruitment. The
12 study participants for these products, they
13 typically include individuals with prior experience
14 using similar drugs.
15 We think that this may increase the
16 sensitivity of this study, and this is because
17 experienced drug users are often better qualified
18 to describe and evaluate subjective effects of
19 drugs of abuse. This is the same way you may look
20 to an experienced food critic when choosing a
21 particular restaurant to dine at. Also, for many
22 participants, they may find study drugs aversive.

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1 To find participants, recruitment usually
2 employs standard methodologies. We're talking
3 about media advertisements: newspaper, magazine
4 ads, ads on Facebook and Craigslist, but we can
5 also use techniques like snowball sampling and
6 refer-a-friend recruiting incentives. Drug users
7 often run in similar peer groups, so if we're able
8 to recruit one or two, often they have a friend
9 that may also be interested.
10 Once we begin recruiting subjects,
11 participants undergo screening procedures, and this
12 helps determine their study eligibility. It
13 includes a medical examination. Participants in
14 these studies, other than their drug use, they're
15 generally healthy, and we exclude those that have
16 significant medical conditions.
17 Once we've identified potential recruits, a
18 qualification or prescreening session is usually
19 employed, and this session involves administration
20 of the placebo along with an intermediate dose of
21 the positive control. We do this to ensure that
22 participants reliably report both liking and

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1 positive effects from the positive control. We
2 wouldn't want you to go to all the trouble of
3 enrolling a subject if they didn't like the
4 positive control comparator.
5 The basic procedures for the HAP studies is
6 usually they're done under double-blind conditions,
7 double-dummy, and they employ it within subject
8 designs, where each subject receives all doses of
9 the drug. During study sessions, ratings of drug
10 liking and other effects, they're assessed
11 repeatedly using a visual analog scale. I'll show
12 you an example of that momentarily.
13 In these studies, peak ratings of liking,
14 they're usually the primary outcome measure,
15 although we can add psychomotor measures. So we
16 can do things like measure the hand-eye
17 coordination of subjects, changes in cognitive
18 ability, and this helps us gather information on
19 the consequences of abuse of the new or
20 investigative drug.
21 We can do two things. We can see the
22 liability of abuse; that is how likely it is a

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1 participant may have used a particular drug and
2 also the consequences of that abuse. So we can get
3 information on whether subjects will be completely
4 sedated and whether they will experience cognitive
5 impairment and other effects. Using these
6 measures, the abuse liability of the test drug is
7 assessed by comparing its effects with those of the
8 placebo and the positive control.
9 Here's the visual analog scale. This
10 appears to subjects on a computer screen, and
11 there's a question here that says, "Do you like the
12 drug?" The subject will take that red line and
13 point to an area on this scale, depicting what they
14 think; so all the way to the right, if you really
15 like the drug effect, or they can click all the way
16 to the left for, "No, not at all."
17 When we're determining liking the drug, we
18 can ask any number of questions. Typically, we can
19 employ upwards of 50 to 20 visual analog scales.
20 We can ask subjects if they like the drug; if it
21 makes them sleepy; if it makes them feel sick; if
22 they're becoming confused, et cetera. Using these

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1 scales, we can capture the subjective profile of
2 the drug.
3 We have to select our dose just like any
4 other clinical study, and as you probably expect,
5 the dose selection in these abuse liability studies
6 is justified, though we typically include
7 suprathreshold doses of the test drug. Often we
8 want to examine about 2 to 3 times the therapeutic
9 dose of the drug, but we'll base our dose
10 evaluation on the data that we have. In these
11 studies, multiple doses of the new drug and the
12 positive control, they're assessed to determine
13 location of the dose-response curve.
14 So it looks like this. On the X-axis here
15 is dose and on the Y-axis is liking, and usually we
16 want to do at least 3 doses to generate a
17 dose-response curve. Unlike the preclinical
18 studies, we want to do our best to stay on the
19 ascending portion of the curve mostly for safety
20 reasons because we don't want to begin dosing
21 extremely high to make subject sick or have them
22 experience other adverse events.

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1 This is the cartoon image of a human abuse
2 liability lab. You can probably tell from the CRT
3 monitors this is a bit dated photo. But subjects
4 will typically sit in front of a monitor, dose in
5 the morning with a drug, and then they can fill out
6 those visual analog scale assessments throughout
7 the day via computer.
8 So what do the data look like from these
9 studies? Here are some of the examples of typical
10 outcome measures in a HAP study, and these data are
11 from Stoops et al. from 2010.
12 What we're looking at here are visual analog
13 scale scores from the intravenous administration of
14 morphine. On the X-axis of both of these graphs is
15 time - this is a time-course assessment - and on
16 the Y-axis is the visual analog scale score.
17 We're looking at two outcome measures. On
18 the left is how much do you like the drug and on
19 the right is, do you feel any drug effect
20 whatsoever? The placebo condition is represented
21 by the open circle, followed by increasing doses of
22 morphine by the square, the triangle, and

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1 upside-down triangle.
2 So I'll walk you through this quickly. We
3 see that when subject started administering
4 placebo, we get the response that we would expect.
5 Subjects do not report very much liking, nor did
6 they report feeling any drug effect. However, as
7 we begin to increase the dose of IV morphine, we
8 see that we can get some nice dose-related
9 increases in both liking and in subjects reporting
10 that they feel the drug effect.
11 Those data are important because peak
12 ratings of liking, well, they often correlate well
13 with pharmacokinetic parameters, things like peak
14 concentration of drug or Cmax. In general, drugs
15 that have a faster rate of onset have an increased
16 abuse potential. I apologize for the size of these
17 graphs, but I want to drive home that point with
18 these data here.
19 These are some data on a study of placebo
20 and hydrocodone. In this study, we're looking at
21 hydrocodone immediate release, hydrocodone extended
22 release that has been crushed, which is the light

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1 green, and hydrocodone extended release that has
2 been left intact. Across these three formulations,
3 we expect that we'll get a difference in the
4 pharmacokinetics.
5 Looking at the top graph, this is actually a
6 visual analog scale score graph. It's very similar
7 to the graphs from the previous slide. And we can
8 see that when we administer immediate-release
9 hydrocodone, it results in a rather rapid onset
10 with liking reported very soon after
11 administration. By way of comparison, you get a
12 smaller peak increase in at-the-moment liking
13 following the administration of the crushed
14 hydrocodone extended release and the intact
15 formulation.
16 Now, the take-home point here is depicted in
17 the bottom graph. On the bottom graph, we see the
18 same time course, but instead of looking at the
19 visual analog scale liking scores, we're looking at
20 drug plasma levels taken after administration.
21 So what we see here is that the
22 immediate-release hydrocodone produces the largest

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1 increase, or Cmax-, mean plasma levels, followed by
2 the crushed extended-release hydrocodone, and the
3 intact extended-release hydrocodone. We see that
4 the liking scales on the top graph, they closely
5 follow the plasma levels depicted on the bottom
6 graph.
7 Here's the same data from the prior slide,
8 but you're just looking at average scores. Again,
9 on that Y-axis is the Emax, or maximum rating of
10 liking, and on the Y-axis [sic] is the actual drug
11 condition. So we can see that the immediate
12 release, which produces the largest Cmax- value,
13 produces the greatest amount of liking, followed by
14 the crushed hydrocodone, and finally the intact
15 hydrocodone.
16 How are these data relevant to MMEs? Well,
17 the preclinical self-administration studies offer
18 us critical variables that could be relevant to
19 MMEs, including whether a drug or opioid is
20 reinforcing. Does it produce an effect that an
21 animal wants to self-administer and experience
22 again? But the preclinical studies also offer

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1 information on both potency and the range of doses
2 that are potentially reinforcing.
3 The clinical or human abuse potential
4 studies offer the face valid, comprehensive
5 assessment of abuse potential, the reinforcement
6 effects of a drug across a range of doses. It can
7 also give us information of the reinforcement
8 effects relative to the therapeutic dose and known
9 positive control.
10 However, the one drawback is that HAP
11 studies, typically they're limited to a relatively
12 small number of comparators. Usually, though not
13 always, as we'll see in some of the upcoming
14 presentations, we're only looking at two drugs in a
15 6-arm study, so 3 doses of a test drug, 2 doses of
16 a positive comparator, and a placebo condition.
17 In conclusion, both the self-administration
18 and HAP procedures, they're relatively standard
19 abuse potential assessment assays that could be
20 useful on any calculation. For MMEs, an ideal
21 situation with respect to abuse is identifying an
22 opioid where the recreational or reinforcing

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1 effects occur at doses that are much higher than
2 efficacious doses.
3 I will show you that on this final slide
4 here, these are completely hypothetical data
5 showing the standard dose-effect curve. In green,
6 you see the therapeutic efficacy of a particular
7 drug for any outcome measure that you want, and on
8 the red, the red lines depict a series of
9 hypothetical abuse-related effects.
10 Starting from left to right, in that first
11 condition, we see a scenario where the
12 abuse-related effects actually occur at doses below
13 the maximum therapeutic efficacy. Moving to the
14 right, one more line, we see a hypothetical drug
15 where the abuse-related effects are shifted
16 slightly to the right and where the therapeutic
17 efficacy occurs prior to the emergence of
18 abuse-related effects, and this is a more ideal
19 situation.
20 But as we move to the right even further, we
21 see similar dose-response curves where the
22 abuse-related effects increase, but they're

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1 relatively further to the right of the therapeutic
2 efficacy. So these lines to the right represent a
3 more ideal situation, where the abuse-related
4 effects occur at doses much higher than the
5 therapeutic efficacy. Thank you very much.
6 Clarifying Questions to Speakers
7 DR. CHAI: Thank you, Dr. Reissig. That was
8 a very thorough coverage of a topic that many of us
9 are not really familiar with, so thank you for
10 taking the time to walk us through that.
11 What we have now is the clarifying questions
12 session. What we'll do is open up to the full
13 panel to ask clarifying questions of this session's
14 speakers. Please note we'll take a break after
15 there are no more clarifying questions, and we are
16 a little bit ahead of time.
17 (Audio feedback.)
18 DR. CHAI: I think there is some feedback;
19 if everyone could mute their phones if they're not
20 speaking.
21 To remind everyone how we'll conduct this
22 clarifying session, please use the raised-hand icon

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1 to indicate when you have a question, and please
2 remember to clear the icon after you've stated your
3 question. When acknowledged, please state your
4 name before you speak and direct your question to a
5 specific presenter, if you can. If you wish for a
6 specific slide, we may or may not be able to find
7 it, but please, if you could describe the content
8 of what you're referring to is.
9 Finally, it would be helpful to acknowledge
10 the end of your question with, "Thank you," and end
11 your follow-up question with, "That is all for my
12 questions," so we can move on to the next panel;
13 and as a gentle reminder, if you could please wait
14 to be acknowledged to speak before you ask your
15 question.
16 Are there any raised hands at this time? I
17 think I see a question.
18 Dr. Bettinger, please unmute your phone.
19 DR. BETTINGER: Hey, Grace. Hopefully you
20 can hear me ok.
21 DR. CHAI: Yes, I can hear you.
22 DR. BETTINGER: I had a question -- or two

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1 here, actually -- hopefully, again, more clarifying
2 because I know we have some time for more
3 discussion later.
4 First of all, great presentations so far.
5 The first one is more directed toward Dr. Mellon
6 and Dr. Volpe just regarding -- Dr. Mellon was
7 really doing a great job clarifying the
8 difficulties in assessing, it sounded, more acute
9 forms of analgesia in human versus animal models.
10 But with some of the emerging knowledge we
11 have in terms of the differences in pain pathways
12 that emerge in the development of chronic pain, in
13 your experience, do you feel that we have models
14 that we can assess opioids in terms of these
15 activities in chronic pain models as opposed to
16 just the, I think, acute pain models, especially
17 from an animal perspective? Thank you.
18 DR. CHAI: That's a great question.
19 Dr. Mellon or Dr. Volpe, could you take that
20 one? Thank you.
21 DR. MELLON: Sure. This is Dan Mellon.
22 That's an excellent question. Clearly, there are

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1 ways that one could do that in nonclinical studies
2 to get a better understanding of the development of
3 tolerance that can occur over time.
4 In the pharmaceutical world, when it comes
5 to drug development, a lot of those studies are
6 typically not actually done. Many of the drug
7 companies will look at more of an acute pain model
8 for proof of concept, knowing that they will
9 actually be able to assess the durability of the
10 effect and understand the potential changes that
11 can occur with repeated application of the product
12 in the clinical setting.
13 There are clearly models that could be done
14 out there, but a vast majority of these compounds,
15 many of which are very old, probably do lack some
16 of those to be able to truly understand the rate of
17 change, if you would, the rate of development of
18 tolerance, the rate, perhaps, of development of
19 hyperalgesia, which is always a challenge when it
20 comes to opioids, to better understand those.
21 I think that's an excellent point. It is
22 certainly something that would have to be taken

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1 studies -- because I've tried to do some research
2 in writing around abuse liability studies
3 themselves -- one thing I've noticed is that a lot
4 of abuse studies seem to just be in either
5 patients -- healthy subjects - or in patients with
6 substance-use disorders.
7 In your opinion, is there quality evidence
8 out there of these studies being performed in
9 patients with either acute pain and chronic pain?
10 Again, in your opinion, do you feel that abuse
11 liability could be different in those patients
12 that, again, are suffering from different types of
13 pain? Thank you.
14 DR. CHAI: Thank you.
15 Dr. Reissig, would you like to handle that
16 question?
17 DR. REISSIG: I'm muted. Okay. Thanks.
18 I'm unmuted now.
19 Yes. I think that's a great question.
20 Typically, when we design human abuse potential
21 studies, one of the reasons we use recreational
22 users is because we think they're the population

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1 into consideration if we were going to try to put
2 that information into the context of the clinical
3 setting, which is of course the vast majority of
4 chronic pain situations that you would be working
5 with.
6 That's all that I can contribute at this
7 point in time on that particular topic. If you'd
8 like to ask additional questions, we can certainly
9 entertain them.
10 DR. CHAI: Thank you, Dr. Mellon. That was
11 great.
12 Dr. Bettinger, did you have follow-up
13 questions to that?
14 DR. BETTINGER: Not to that. I had a
15 separate question, but that was a great answer.
16 Again, I was assuming that answer, but I wanted to,
17 again, just clarify it, especially for, of course,
18 our audience, too.
19 My second question, real briefly, was for
20 Dr. Reissig, if I'm able to; I was checking.
21 Again, a similar style of a question in
22 terms of when we're looking at these

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1 most likely to abuse a drug. We also think that
2 since they had the most experience in using
3 recreational drugs, they're a great population to
4 assess abuse liability in them.
5 I think your question about pain in patients
6 is an empirical one. Typically, for drug
7 development, we would not require a human abuse
8 potential study in pain patients specifically;
9 they're always done in recreational users. I don't
10 know how those two populations would differ, but I
11 suspect that, certainly, there could be differences
12 in them, and we might run into other complications
13 when assessing something like liking, for example.
14 So if you're constantly in pain, the
15 analgesia produced on an opioid could be desirable,
16 and someone may say, "Yes, I like that effect."
17 It's an interesting question whether that type of
18 liking, how or whether it differs from the type of
19 liking that's sought after by a recreational user.
20 DR. CHAI: Thank you, Dr. Reissig.
21 Dr. Bettinger, did you have any follow-up
22 questions?

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1 DR. BETTINGER: No, no. I appreciate the
2 clarification there and really appreciate it.
3 Thank you.
4 DR. CHAI: Thank you.
5 I see the next question from Dr. Comer.
6 Please go ahead.
7 DR. COMER: Hi. Thank you. My question is
8 for Dr. Reissig.
9 You were talking about the calculations of
10 MMEs for abuse liability-related endpoints, but I'm
11 wondering if you could clarify -- because I was
12 just trying to wrap my head around that idea, and I
13 know it's an important one. But how does it relate
14 back to calculating MMEs for analgesia?
15 Are you thinking that the MME abuse
16 liability assessments are very close to the MMEs
17 for analgesia, then that would be a bad situation,
18 whereas the drug that has a wide separation for
19 those two endpoints, that would be the -- is that
20 what you're talking about?
21 DR. REISSIG: Yes. That's another good
22 question. To my knowledge, abuse liability

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1 considerations have not been taken into account for
2 the current MME calculations. I think the abuse
3 liability assessment is just one parameter that
4 could be taken into context.
5 As you may have alluded to, if we have two
6 opioids that produce equal efficacy in analgesia or
7 pain relief, I think there are a variety of
8 outcomes we could use in order to determine the
9 best selection. I think an abuse liability
10 assessment is just one parameter.
11 So for sure, I think if, hypothetically, two
12 drugs produce equal efficacy, we would want to
13 select the one that had a wider therapeutic window
14 with respect to abuse potential.
15 Does that answer your question?
16 DR. COMER: Yes, it does. I think you sort
17 of touched on this a little bit as well, or someone
18 did in one of the sessions this morning or talks
19 this morning. The adverse effects are also another
20 really critical aspect of calculating MMEs because
21 those three endpoints of analgesia, abuse
22 liability, and respiratory depression, for example,

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1 if something has a very wide separation across all
2 of those potency estimates, then that would be
3 great, but if they're all tightly connected, like
4 with fentanyl, for example, then that would be a
5 really dangerous situation.
6 DR. REISSIG: Right. Yes. No, I totally
7 agree. I think abuse liability is just one
8 potential parameter. As you mentioned, respiratory
9 depression is another important one.
10 DR. COMER: Yes. I think we need to do that
11 research. It would be nice to have a table like
12 that. Thank you.
13 DR. CHAI: Thank you, Dr. Comer and
14 Dr. Reissig.
15 I see a next question for Dr. Zhang. Please
16 go ahead.
17 (No response.)
18 DR. CHAI: You may be on mute.
19 DR. ZHANG: Hi, Grace. Can you hear me?
20 DR. CHAI: Yes.
21 DR. ZHANG: Thank you so much.
22 Thanks for all the great presentations from

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1 FDA this morning so far. This is Kun Zhang from
2 CDC. I have a question for Dr. O'Donnell.
3 I saw you used the labeling of Hysingla
4 extended release as an example, showing the oral
5 conversion factors from Hysingla to other types of
6 opioids. Just out of curiosity, I know there's
7 another extended-release hydrocodone product on the
8 market, which is I think Zohydro.
9 I just looked up the labeling for that drug.
10 It's interesting to see, for even two -- which I
11 think is the same type of opioid, which has the
12 same suggested starting dose, both at 20 milligram
13 per day, but they do have different conversion
14 tables to other opioids. For instance, they have
15 different conversion factors to oxymorphone and
16 different conversion factors to methadone.
17 I guess as a prescriber or clinician, when
18 choosing between these two drugs, how to make sense
19 of the different types of conversion factors.
20 DR. CHAI: Thank you.
21 Dr. O'Donnell?
22 DR. O'DONNELL: Yes. Actually, those

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1 conversion tables in the labels were actually from
2 the other opioid to the investigational product;
3 it's unidirectional. They were used in clinical
4 trials, as I mentioned, in the open-label titration
5 phases and submitted in the application. The FDA
6 did not generate the conversion tables.
7 DR. ZHANG: Okay.
8 DR. O'DONNELL: So they were clinical trial
9 data, specifically.
10 DR. ZHANG: Okay. Thank you.
11 DR. CHAI: Thank you.
12 I see Dr. Fine next.
13 DR. FINE: Yes. Can you hear me alright?
14 DR. CHAI: Yes. Could you please state your
15 name and let us know who your question is directed
16 to?
17 DR. FINE: Right. Thank you. I just want
18 to make sure I was able to be audible. Yes. This
19 is Perry Fine, University of Utah. My question is
20 for Dr. Reissig, and it's actually a follow-up from
21 Dr. Bettinger.
22 Are we able to pull up Dr. Reissig's last

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1 slide with the modeling of analgesia versus abuse,
2 the green and red lines?
3 Great. Thank you.
4 In the literature, and certainly in the
5 current media and other places, there's a lot of
6 questioning of this phenomenon that over the course
7 of the years has been called pseudoaddiction, and
8 there seems to be an effort to discount the
9 phenomenon, even though it was never experimentally
10 demonstrated.
11 This slides seems to sort of beg the
12 question and, Dr. Reissig, is there any way to
13 distinguish -- in a person who is on opioid therapy
14 experiencing analgesia at end of dose, as blood and
15 brain levels go down, who's starting to have a
16 resurgence of pain, given the emotional or the
17 affective components of pain, as well as of
18 opioids, is there truly any way to distinguish, or
19 a model that could distinguish, the individual's
20 response to a resurgence of pain and the emotional
21 consequences of that, and a desire then to leave
22 that with taking a drug from what would be

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1 attributed to an abuse, or a craving, or a drug
2 liking, independent of pain?
3 I hope I've articulated that adequately, but
4 if not, we can try and dig into it. But I hope you
5 understand what I'm trying to get at here.
6 DR. REISSIG: Yes. I think that's a great
7 question. I'm not an expert on opioid withdrawal,
8 so I think we would need to take a look at some of
9 the opioid withdrawal scales that are often used to
10 evaluate that, and then examine the amount of
11 overlap that there might be with those reinforcing
12 effects. And I suspect there may be some
13 challenges in disentangling those two things.
14 DR. FINE: Thank you.
15 DR. CHAI: Did you have any follow-up
16 questions, Dr. Fine.
17 Thank you, Dr. Reissig for the answer.
18 DR. FINE: No. I'm wondering if anybody
19 else on the panel has any insight into that. I
20 think this is a really interesting slide. I'm
21 wondering if there's a convergence on therapeutic
22 efficacy and hypothetical abuse-related effects

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1 that are actually indistinguishable; in other
2 words, is there another line where there's an
3 overlap in terms of the actual human experience?
4 We heard a lot from the public yesterday in
5 the commentary section about perception of abuse
6 versus adequate pain relief, and I'm wondering if
7 Dr. Reissig has additional thoughts on how maybe to
8 integrate this slide, or the model, or whatever
9 it's trying to show, in terms of effective dose in
10 a more integrated way.
11 DR. CHAI: Did you want to take that one,
12 Dr. Reissig?
13 DR. REISSIG: Yes, sure. I can only offer
14 my personal speculation, but I think there probably
15 is some overlap in therapeutic efficacy and
16 reinforcing effects. Often pain relief is
17 accompanied by good effects or liking, so I
18 wouldn't be surprised if there's some overlap.
19 Thank you.
20 DR. CHAI: Thank you.
21 DR. FINE: Thank you.
22 DR. CHAI: Thank you, Dr. Fine, as well.

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1 Dr. Comer, did you have a new question or
2 were you adding on?
3 DR. COMER: No. I was just going to maybe
4 provide some response to Dr. Fine's question.
5 DR. CHAI: Great.
6 DR. COMER: Basically, what we're talking
7 about are negative reinforcing effects. That's
8 what we describe as increase in behavior due to
9 removal of an aversive stimulus. You're talking
10 about pain. You've also touched upon opioid
11 withdrawal. This is an area that I think is really
12 critical and one that George Koob has often talked
13 about. He's the head of NIAAA.
14 We do have some data in our lab with heroin
15 users. I did a study a long time ago to compare
16 the relative reinforcing and subjective effects of
17 methadone versus buprenorphine. I was curious to
18 see what these drugs look like in non-dependent
19 people, so I brought in hero-independent people,
20 detoxed them in the hospital, and then started
21 doing testing. What I noticed was that at doses
22 that produced very little ratings of drug liking,

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1 the self-administration was really high.
2 One of the big advantages of working with
3 human research volunteers is you can ask them why
4 they did what they did. What they most often told
5 me was, yeah, they didn't really feel the effects
6 of the drug anymore, but it was taking away their
7 low back pain. It was helping them sleep better at
8 night, so that's why they were self-administering
9 the drug.
10 So that question that you asked I think is
11 very important with regard to patients in pain, and
12 I do think we need to do a lot more research on
13 this topic.
14 DR. CHAI: Thank you, Dr. Comer.
15 Ms. Cowan, do you have the next question?
16 MS. COWAN: Yes. What I'm hearing is in
17 testing these drugs, they use addicts, people who
18 are already using them, and yet I really believe
19 that people with pain are very different because
20 there are so many other components.
21 So I wonder why they have never really used
22 a sample of actual people living with pain to test

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1 the liking or the effects of these drugs. It
2 bothers me. I think it sort of plays into only
3 increasing the stigma around pain when you stand
4 back and look at it from a public eye, and maybe
5 even a practitioner eye. It just seems like it's
6 not a balanced way to look at the liking and impact
7 of these medications. Thank you.
8 DR. CHAI: Thank you, Ms. Cowan.
9 Dr. Comer, did you have a follow-up
10 question?
11 DR. COMER: No. I just had a response to
12 Penney's comment.
13 DR. CHAI: Okay.
14 DR. COMER: It's really difficult to do
15 those studies, and I think that's partly why so few
16 have been done. There's an old one by Lasagna and
17 colleagues where they did do that, and they were
18 reporting that the pain responses were different in
19 people who had chronic pain and the normal healthy
20 volunteers.
21 I did a study to try to capture this
22 phenomenon in people who were normal healthy

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1 volunteers versus drug users who are in
2 experimentally induced pain, so they were in a cold
3 pressor test paradigm where they would repeatedly,
4 be experiencing pain versus no pain.
5 What I found under those conditions was that
6 drug liking was very similar in the non-drug users
7 and the ones who were recreational users, and also
8 in the pain condition versus the - but they did
9 differ, for the normal healthy volunteers, in the
10 pain versus the non-pain condition.
11 The drug users under both pain and no pain
12 liked the drugs regardless. The non-drug users
13 didn't really like the drugs when they were not in
14 pain, but they liked it and self-administered it
15 when they were in pain. So that's different than a
16 patient with clinical pain, of course, but that was
17 sort of an attempt to kind of get at that question.
18 MS. COWAN: I guess my point, or part of my
19 question, is when you look at a person with pain,
20 it's not just about their pain. There are so many
21 other things that impact that level of pain. And
22 we're not looking at any of those, doing the

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1 biopsychosocial, all those impacts that impact how
2 they're suffering.
3 I don't know if the drug would have an
4 effect on any of that or play in it; so if I could
5 see the surveys of all of these components to
6 really understand what's going on with the
7 individual, and then during the same testing.
8 So I'm just wondering if anybody's ever done
9 that or thought about it. It just seems, to me,
10 there are differences that you have to stand back
11 and look at in how to design that, and hopefully
12 somebody will do it. Thank you.
13 DR. CHAI: Thank you, Ms. Cowan, and thank
14 you, Dr. Comer.
15 Are there any other clarifying questions at
16 this time?
17 (No response.)
18 DR. CHAI: What we'll do now is take a quick
19 10-minute break. So we'll come back and reconvene
20 at 11:05, and we'll jump right into Dr. Babalonis'
21 presentation. So thank you, and see you in
22 10 minutes.

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1 (Whereupon, at 10:54 a.m., a recess was
2 taken.)
3 DR. CHAI: Welcome back, everyone. This has
4 been a fantastic morning so far and really looking
5 forward to the next session.
6 Dr. Shanna Babalonis will be presenting
7 next, and she will be providing highlights from an
8 ongoing study on the relative potency of
9 oxymorphone compared to other new opioid
10 antagonists in humans.
11 Thank you, Dr. Babalonis.
12 Presentation – Shanna Babalonis
13 DR. BABALONIS: Thank you so much, and also
14 thank you to Dr. Reissig, who provided a great
15 context and background for this presentation.
16 I'll be presenting the results of two human
17 abuse potential studies that were conducted to
18 examine the relative potency of both oral and
19 intravenous oxymorphone compared to other mu opioid
20 antagonists. I have no conflicts of interest
21 related to the present work.
22 Oxymorphone is a semisynthetic opioid

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1 antagonist which exhibits a high degree of
2 mu opioid receptor selectivity and intrinsic
3 activity, as we heard Dr. Mellon present earlier.
4 Oral and parenteral formulations of oxymorphone
5 were initially approved by the FDA in 1959 under
6 the trade name Numorphan. However, in 1979, the
7 manufacturer voluntarily removed the oral product,
8 citing commercial reasons, but there were reports
9 at the time of high rates of misuse, particularly
10 intravenous use.
11 Oral oxymorphone returned to the market in
12 2006 under the new trade names Opana and Opana ER.
13 Since this time, oxymorphone misuse has increased,
14 and the extended-release product was removed from
15 the market due to risks associated with this
16 misuse. However, there are really little
17 controlled data available on the abuse potential of
18 oxymorphone.
19 These two studies will examine
20 within-subject, double-blind, and placebo-
21 controlled studies to examine the relative abuse
22 potential and relative potency of oral oxymorphone

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1 and the relative abuse potential and potency of
2 intravenous oxymorphone. I'll start with the oral
3 study.
4 The published potency and conversion
5 estimates of oral oxymorphone are based on several
6 clinical trials with pain patients, and an example
7 of these conversions are listed in the table here.
8 This table indicates that oral oxymorphone is more
9 potent than all those listed comparators, so twice
10 as potent as oral oxycodone, hydrocodone, and
11 methadone, and 3 times as potent as oral morphine.
12 However, again, we have limited studies available
13 on the abuse potential of this oral product.
14 One previous study examined the
15 pharmacodynamic effects of oral oxymorphone. It
16 was an abuse liability study to look at
17 extended-release oxymorphone relative to extended-
18 release oxycodone, and those doses were based on
19 the equianalgesic estimates in conversion tables,
20 so the doses were 2 to 1 oxycodone to oxymorphone.
21 In this abuse liability study, the authors
22 concluded that oxymorphone had less abuse liability

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1 than oxycodone. However, when we inspected the
2 data quite closely, we saw that comparable dose
3 ranges weren't evaluated. For example, when we
4 looked at pupil diameter measurements, which are
5 often thought of as being a signal of the opioid
6 agonist efficacy, they were not comparable across
7 the matched-dose conditions, indicating that 2 to 1
8 ratio might be off.

9 So we wanted to follow up on that trial and
10 conduct a comprehensive study on oral oxymorphone.
11 The aims of that study were to examine the relative
12 abuse liability and potency of oral oxymorphone
13 compared to oxycodone, employing a broader range of
14 pharmacodynamic measures, and the other aim was to
15 examine the analgesic response to both drugs using
16 two experimental pain models.

17 Our participants were healthy adults who
18 misused opioids but who are not physically
19 dependent on opioids. This was a randomized
20 within-subject crossover design, placebo-controlled
21 design, and participants resided as inpatients for
22 approximately 3 weeks and completed a total of

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1 7 experimental sessions. Each session was
2 separated by at least 48 hours.

3 For our study, we elected to use equal doses
4 of oxycodone and oxymorphone across a 4fold range
5 of oral doses, so we tested oxymorphone 10, 20, and
6 40 milligrams and oxycodone 10, 20, and
7 40 milligrams, and placebo. We collected a variety
8 of outcome measures, including physiological
9 assessments, pain assessments, subjective and
10 abuse-potential measures, and observer-rated
11 measures.

12 We analyzed the data also for relative
13 potency, so we used the Finney parallel lines
14 bioassay to look at the relative potency of these
15 two compounds.

16 This graph displays pupil diameter
17 measurements for oxycodone in the left panel and
18 oxymorphone on the right. In the legend up above,
19 the doses will be a circle for placebo, a triangle
20 for 10 milligrams, a diamond for 20, and a square
21 for 40 milligrams. The data are going to be
22 displayed across time, from baseline to 6 hours

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1 after drug administration. Keep in mind, for pupil
2 diameter, lower values on this graph will indicate
3 a greater mu opioid-related response.

4 This is the data for placebo and
5 10 milligrams. Already, the 10-milligram dose of
6 oxycodone is showing a greater effect than
7 oxymorphone, with the filled symbols indicating a
8 significant difference from placebo. This is the
9 20-milligram doses and the 40-milligram dose.

10 Overall, what you can conceive is that these
11 data suggest that oral oxycodone is approximately
12 twice as potent as oral oxymorphone. For example,
13 20 milligrams of oxycodone, on the left in
14 diamonds, is producing an effect that appears
15 roughly equivalent to the 40-milligram dose of
16 oxymorphone, on the right. These data suggest,
17 again, that oral oxycodone may be twice as potent
18 as oral oxymorphone, which is the opposite
19 relationship from the conversion tables.

20 This slide presents peak concentrations of
21 end-tidal carbon dioxide, which is a measure of
22 respiratory depression. Higher values on this

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1 graph indicate greater respiratory depression.
2 These data are presented as a function of dose on
3 the X-axis.

4 The oxycodone, in the white symbols, dose
5 dependently increases respiratory depression, with
6 the 40-milligram dose producing significant effects
7 greater than oxymorphone, with the asterisks
8 indicating a significant difference between the two
9 compounds and filled symbols indicating a
10 significant difference from placebo.

11 We also conducted two experimental pain
12 assessments. We conducted a cold pressor, where
13 participants submerged their arm into cold water,
14 and we did a pressure algometer, where pressure is
15 applied to the palm of the hand. We collected two
16 outcome measures, threshold, which is a point at
17 which pain is detected, and tolerance, the point at
18 which pain is no longer tolerable.

19 On the left panel, oxycodone here increased
20 the latency for participants to detect cold pain
21 and acted as an analgesic, while oxymorphone
22 produced minimal effects. On the right panel, the

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1 high doses of both drugs increased the total time
2 participants could leave their arm in cold water,
3 with oxycodone perhaps just producing maybe a
4 slightly greater analgesic effect. Similar
5 outcomes occurred on pressure pain. Oxycodone
6 dose-dependently increased the analgesic effects,
7 while oxymorphone was roughly placebo-like.
8 This slide displays the visual analog
9 ratings of the item, "Do you like the drug effect?"
10 again with oxycodone on the left and oxymorphone on
11 the right. This is data displayed across time
12 through 6 hours post-dose.
13 These are the data for 10 milligrams,
14 20 milligrams, and 40 milligrams. Here we can see
15 that at the highest dose tested, 40 milligrams, the
16 effects of the drug seemed somewhat comparable. If
17 we look at participant ratings of street value, on
18 the left, how much would participants pay on the
19 street for the drug they received, oxycodone, in
20 white symbols, again appears to produce greater
21 effects. But its highest dose, again, the effects
22 appear somewhat similar to oxymorphone, in yellow.

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1 When trained observers rate opioid agonist effects,
2 oxycodone produces greater observable effects.
3 Again, we conducted relative potency
4 assessments on most outcomes, however, several
5 outcomes were invalid due to the substantially
6 greater effects of oxycodone. But in general,
7 oxycodone was 2-fold more potent on pain outcomes
8 and 1.2-fold more potent on subjective outcomes.
9 For things like pupil diameter, that was an
10 invalid comparison on this model, however, we can
11 visually assess that oxycodone was 2-fold more
12 potent than oxymorphone. So again, these data are
13 in contrast to the MME conversion tables, which
14 suggest the opposite relationship, that oxymorphone
15 is 2-fold more potent than oxycodone.
16 To summarize this study, oral oxymorphone is
17 actually less potent than oxycodone on a broad
18 array of measures, including experimental pain
19 outcomes. And again, these findings are in
20 conflict with the published potency ratios derived
21 from clinical pain studies. However, one
22 contributing factor is the low bioavailability of

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1 oral oxymorphone, which is approximately
2 10 percent, compared to the relatively high
3 bioavailability of oxycodone, which is estimated
4 between 60 and 87 percent. However, very
5 interestingly, at higher doses, the abuse potential
6 appeared somewhat similar to oxycodone.
7 In this study, we highlight the effects of
8 experimental pain. If one accepts the analgesic
9 potency estimates from clinical trials as the
10 accurate assessment, it may in turn be that these
11 are not predictive of relative potency for other
12 pharmacodynamic actions, including abuse potential.
13 However, if we looked at experimentally induced
14 pain as a valid assay for analgesia, such as this
15 study, then oxymorphone may have greater abuse
16 liability than oxycodone at equianalgesic doses.
17 In order to fully characterize the abuse
18 liability of oxymorphone, we wanted to look at a
19 broader range of doses in routes of administration
20 to fully answer this question, which brings us to
21 study 2, where we looked at the relative abuse
22 potential and relative potency of intravenous

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1 oxymorphone.
2 Again, just to highlight the background of
3 intravenous oxymorphone, initially in the 1970s,
4 prior to the initial removal of Numorphan from the
5 U.S. market, there were documented cases of opioid
6 users injecting oxymorphone, and some reported
7 preferring oxymorphone over heroin when injected.
8 Since the reintroduction of the oxymorphone
9 products onto the market in 2006 when Opana was
10 introduced, oxymorphone has been misused via the IV
11 route at a disproportionately high rate compared to
12 other prescription opioids.
13 IV oxymorphone has been associated with
14 significant public health harms, including an HIV
15 outbreak in rural Indiana in which 80 percent of
16 infected individuals reported injecting
17 oxymorphone, and also acute kidney injury and blood
18 vessel and blood clotting disorders, with these
19 latter two conditions being associated more with
20 the excipients that are embedded into extended-
21 release oxymorphone rather than the parent compound
22 itself.

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1 Due to these safety concerns, FDA requested
2 the removal of Opana ER from the market in 2017,
3 and the manufacturer ultimately complied. However,
4 generic formulations of both immediate and
5 extended-release products remain on the market, and
6 no controlled data are available on the abuse
7 potential of IV oxymorphone.
8 The primary aims of this dose-finding,
9 double-blind, placebo-controlled, two-site study
10 was to compare IV oxymorphone to IV morphine,
11 oxycodone, and hydromorphone on an array of abuse
12 potential physiological and observer-rated effects
13 and also to calculate the relative potency of
14 IV oxymorphone on abuse potential and safety and
15 physiological outcomes.
16 This study also served as a pilot study to
17 look at equieffective doses of oxymorphone and the
18 comparator opioids for a study that's going on
19 right now that we're conducting, along with
20 Dr. Comer at Columbia University, to examine
21 IV oxymorphone self-administration, and that
22 study's currently in progress.

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1 The methods for this current study, again,
2 were a two-site, within-subject, double-blind,
3 placebo-controlled, 5-week, inpatient study.
4 Nineteen experimental sessions were conducted with
5 one IV dose administered per session. And data,
6 again, were collected before and for 6 hours after
7 IV dose administration, and sessions were conducted
8 up to 5 days per week.
9 The participants in this study were quite a
10 bit different. These were otherwise healthy adults
11 with moderate to severe opioid-use disorder, with
12 current physical dependence on short-acting opioids
13 and current IV use. The participants in this study
14 were 1 woman and 5 men, 1 African-American and
15 5 Caucasian participants, with a mean age of
16 approximately 33 years and a BMI of approximately
17 22.
18 All were daily cigarette smokers, and the
19 participants in this study were using intravenous
20 heroin and fentanyl primarily as their drugs of
21 choice, and they were using multiple times a day,
22 nearly every day, injecting heroin and fentanyl.

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1 They were also using some other drugs like alcohol,
2 other prescription opioids, cocaine,
3 benzodiazepine, and methamphetamine.
4 Participants were stabilized on oral
5 morphine of 30 milligrams per dose 4 times a day,
6 and during each experimental session, we
7 administered one IV dose, and these doses are
8 expressed as milligrams per 70 kilogram because we
9 adjusted for body weight.
10 We tested a wide array of oxymorphone doses,
11 1.8, 3.2, 5.6, 10, 18, and 32 milligrams; similar
12 doses of hydromorphone, but we ended it at
13 18 milligrams as the highest dose; oxycodone, 18,
14 32, and 56; morphine, 18 and 32; as well as
15 placebo. To give some background on the dose
16 selection, we wanted to test a very wide range of
17 oxymorphone doses, which in previous studies we
18 conducted included up to 18 milligrams of
19 hydromorphone and 50 milligrams of oxycodone and
20 morphine, so we knew that we could safely go to
21 roughly those doses.
22 We also wanted to be sure to include the

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1 estimate for IV morphine, and the MME tables
2 suggested that IV oxymorphone was 10 times as
3 potent as IV morphine with a 1 to 10 comparison.
4 So we included relatively low doses of 1.8, 3.2,
5 5.6 to compare to a 10-fold higher dose range of
6 morphine.
7 Initially, we had included high doses of
8 oxymorphone and morphine, 56 milligrams, but those
9 were withheld on several occasions due to safety
10 concerns, so those data are not presented here.
11 Doses of each drug were randomized in
12 ascending order for safety but were otherwise
13 randomized. Again, our primary outcomes here were
14 safety and physiological outcomes across the wide
15 range of physiological measures and subjective
16 measures of drug effect, including VAS ratings of
17 drug liking and street value. Again, we used a
18 relative potency analysis using the Finney parallel
19 lines bioassay.
20 This graph will display end-tidal CO2 with,
21 again, higher concentrations of end-tidal carbon
22 dioxide as a measure of respiratory depression, so

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1 higher concentrations indicating greater
2 respiratory depression and greater risks. Again,
3 these data are presented as a function of dose on
4 the X-axis, so these are peak effects.
5 On this graph and all slides that follow,
6 doses of the drugs will display as a line function
7 with filled symbols indicating a significant
8 difference from placebo. The first data point here
9 in the circle is placebo and the triangles are
10 morphine. Oxycodone and morphine are producing
11 relatively minimal effects on respiratory
12 depression. Hydromorphone dose-dependently
13 increases concentrations of end-tidal CO₂, with an
14 18-milligram dose being significantly different
15 from placebo. Similar effects were found with
16 oxymorphone, with the two highest doses producing
17 significant effects relative to placebo.
18 This graph will display minimum pupil
19 diameter with smaller values, indicating greater
20 opioid effects. Here morphine produced modest
21 decreases; oxycodone decreased pupil diameter with
22 the highest two doses producing a significant

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1 effect; dose-related decreases from hydromorphone;
2 and oxymorphone producing even greater effects
3 here.
4 This slide presents data from the visual
5 analog question, "Do you like the drug effect
6 you're feeling right now?" This question was
7 presented on a bipolar VAS scale with zero being a
8 strong dislike, 50 being neutral, and 100 being a
9 strong drug liking effect, so this is the only
10 graph that will start at 50 for that reason.
11 Morphine did not produce any significant
12 effects; all doses of oxycodone, pretty significant
13 effects; hydromorphone, all doses were significant
14 except for the lowest dose; and oxymorphone
15 produced effects even greater than those of
16 hydromorphone.
17 This slide presents VAS ratings of the
18 question, "Do you feel high?" These data are
19 presented on a traditional unipolar VAS scale, zero
20 being not at all and 100 being extremely. Again,
21 morphine produced a rather minimal effect; all the
22 oxycodone doses produced significant ratings;

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1 hydromorphone produced increases in ratings
2 particularly at the two highest doses; and every
3 dose tested of oxymorphone produced significant
4 ratings of feeling high.
5 This is the last data slide here. This
6 figure presents participant peak ratings of street
7 value of each of the drug doses, meaning how much
8 would the participants pay on the street for these
9 drug doses.
10 Again, morphine produced relatively low
11 ratings, as did oxycodone; and hydromorphone
12 produced a significant effect at the highest dose
13 tested; whereas oxymorphone, again, produced the
14 greatest ratings with the four highest doses being
15 significantly different from placebo and
16 participants reporting an approximate value of 15
17 to \$20 dollars for each of these doses.
18 We also conducted relative potency analyses.
19 Because we only tested a limited number of morphine
20 doses, we can only compare oxymorphone and
21 hydromorphone, and we examined equal doses of those
22 drugs. We assessed oxymorphone and oxycodone at a

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1 10-fold difference dose range for these bioassays.
2 This is a relative potency of oxymorphone
3 versus hydromorphone. Outcomes with dashes were
4 not valid. Again, that couldn't be compared with
5 this assay due to potency differences. In this
6 table here, on abuse liability outcomes, we see the
7 milligrams of IV oxymorphone that are roughly
8 equivalent to 1 milligram of hydromorphone.
9 For abuse liability outcomes, 0.36 to
10 0.41 milligrams of oxymorphone was equivalent to
11 1 milligram of hydromorphone, and on respiratory
12 depression outcomes, 0.82 milligrams of oxymorphone
13 was equivalent to 1 milligram of hydromorphone.
14 For respiratory depression, oxymorphone was
15 1.2-fold more potent, and for abuse liability,
16 oxymorphone was 2.3 to 2.8-fold more potent than
17 hydromorphone.
18 In oxymorphone versus oxycodone potency
19 analyses -- again, this is milligrams of IV
20 oxymorphone equivalent to 1 milligram of
21 IV oxycodone on abuse liability outcomes -- 0.7 to
22 0.8 milligrams of oxymorphone produced effects

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1 equivalent to 1 milligram of oxycodone, which
2 results in oxymorphone 12.5 to 14-fold more potent
3 than oxycodone.
4 To summarize the study, all of the drugs
5 tested produced prototypical dose-related opioid
6 effects such as miosis and increased end-tidal
7 carbon dioxide. The abuse potential of
8 IV oxymorphone far exceeded all the comparator
9 opioids, with even a moderate dose producing peak
10 effects that were greater than or equal to all
11 other comparator doses. We even saw significant
12 abuse-related effects of oxymorphone at
13 comparatively low doses, so the 1.8 to
14 5.6-milligram dose range.
15 These data align with the surveillance
16 reports, indicating that after adjusting for
17 prescription rates and availability, oxymorphone
18 had been injected at the highest rates relative to
19 other prescription opioids, with some estimates
20 indicating that that's 7 times higher rates of
21 injection of oxymorphone compared to other
22 prescription opioids.

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1 To conclude, these high rates of injection
2 are likely due, again, to the low oral
3 bioavailability of oxymorphone, which we
4 demonstrated in the first study, which may increase
5 misuse by other routes with greater bioavailability
6 such as intravenous use. There's easy manipulation
7 of the oral oxymorphone product to access high
8 doses. Oxymorphone is marketed in pills up to
9 40 milligrams, reinforcing the facts in abuse
10 liability at doses as low as 1.8 milligrams.
11 These results could also be due to the
12 pharmacological action of oxymorphone, including a
13 high degree of binding affinity and intrinsic
14 activity, rapid transport across the blood-brain
15 barrier, and a relative high potency, particularly
16 on abuse outcomes. So overall, oxymorphone may
17 pose a disproportionately high degree of risk and
18 public health harms relative to other full-agonist
19 IV prescription opioids.
20 In conclusion, as we have heard across
21 presentations, both yesterday and today, it is
22 clear that several pharmacological and non-

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1 pharmacological factors can influence relative
2 potency, and MME conversion tables likely don't
3 speak to or predict the safety profiles or the
4 abuse potential of opioids.
5 I would like to conclude by acknowledging
6 the research teams at the University of Kentucky
7 and Columbia, and the funding sources. Thank you.
8 DR. CHAI: Thank you, Dr. Babalonis. That
9 was amazing. Thank you for the preliminary results
10 from these ongoing studies. I think I speak for
11 everyone that we're looking forward to seeing the
12 final study results.
13 Next, we have Dr. Comer, who was also
14 co-lead on this research, who will provide
15 additional insights into the pharmacological and
16 non-pharmacological factors related to opioid
17 potency.
18 Thank you, Dr. Comer.
19 Presentation – Sandra Comer
20 DR. COMER: Good morning, everyone. I'd
21 like to thank the FDA for inviting me to give this
22 presentation and Shanna for presenting the results

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1 of our study.
2 Shanna presented data showing potency
3 relationships for different opioids and different
4 non-analgesic effects. I'd like to take a step
5 back and provide a broader view to talk about both
6 pharmacological and non-pharmacological variables
7 that may impact on calculations of relative
8 potency. I'll be summarizing data from preclinical
9 studies focused on analgesic effects.
10 Of course, the pharmacology of the drug is a
11 really important characteristic. One aspect of
12 pharmacology that I'd like to focus on throughout
13 my talk is efficacy. Efficacy is a property of the
14 drug, but it can be expressed in different ways,
15 depending on the experimental parameters that are
16 used.
17 I was trained as a behavioral
18 pharmacologist, and we spent a lot of time thinking
19 about, and talking about, and running experiments
20 to try to get a handle on this particular effect.
21 What I'm showing here are data from a study
22 that was collected in rats, and just to orient you

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1 to the slide and most of the subsequent slides,
 2 I'll be showing you dose-effect curves, so doses
 3 along the X-axis, and in this particular figure
 4 it's percent maximum possible effect on the Y-axis.
 5 In this study, they assessed analgesic
 6 responses -- or anti-nociceptive responses;
 7 sorry -- in these rats, where the water was
 8 maintained at 50 degrees centigrade, and they just
 9 measured the latency for the animal to flick its
 10 tail out of the water.
 11 You can see that both methadone in the
 12 circles and morphine in the triangles produced a
 13 full analgesic response, but buprenorphine and
 14 nalbuphine did not. All of these four substances
 15 are approved for treating pain. Buprenorphine, as
 16 a partial agonist, it produces I guess about a
 17 30 percent maximal under these experimental
 18 conditions, and nalbuphine didn't really produce
 19 much effect at all. NAQ is another partial agonist
 20 that has been used experimentally.
 21 The red line, the horizontal line that I've
 22 drawn across this figure, shows the ED50 value, so

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1 it's the effective dose at the 50 percent level.
 2 In preclinical studies, this is typically the level
 3 of effect that you use to calculate relative
 4 potency of drugs. But what happens with something
 5 like buprenorphine, it doesn't produce a 50 percent
 6 response. So the question is, do you lower that
 7 red line to something like 30 percent? And if you
 8 do, then the relative potency, the general
 9 relationship still holds, but the actual doses that
 10 you come up with will be different. So that's one
 11 issue that we need to grapple with.
 12 Another factor that we have to pay attention
 13 to is the intensity of the pain. The analgesic
 14 efficacy can differ depending on the intensity or
 15 the type, as well, of pain med that is produced or
 16 being assessed.
 17 I'm showing you here data from a study that
 18 was conducted in rats where they used radiant heat
 19 applied to the hind paw. In the left panel are
 20 effectors for meperidine, the middle is for
 21 morphine, and in the right is buprenorphine. These
 22 drugs were all given subcutaneously, and they used

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1 two different pain intensities. In the closed
 2 symbols, it's low-intensity pain and in the open
 3 symbols, its high-intensity pain.
 4 For all of these drugs, there's either a
 5 rightward or a downward shift in the dose-response
 6 curves. So when the pain intensity is high, it
 7 takes larger doses to produce an analgesic
 8 response, so that kind of makes sense. With
 9 buprenorphine, whereas with the low-intensity
 10 stimulus, it produces a full analgesic response,
 11 under the high-intensity stimulus, it can no longer
 12 produce a full analgesic response.
 13 The intensity of the pain is important, but
 14 the route of administration is also important. We
 15 heard about this yesterday with Dr. McPherson,
 16 that trying to calculate relative potency based on
 17 route of administration can be really complicated,
 18 and this figure illustrates that.
 19 On the top panel, I'm showing you the data
 20 again that I just showed you, the subcutaneous
 21 route of administration. But when you look at
 22 those same drugs given intrathecally, you see a

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1 very different pattern of effect. When given
 2 intrathecally, meperidine produces analgesic
 3 responses that are pretty much the same regardless
 4 of the intensity of the pain. With morphine,
 5 there's maybe a slight rightward shift in the
 6 dose-response curve. But with buprenorphine,
 7 there's basically no analgesic response when it was
 8 given intrathecally under the high-intensity pain
 9 condition.
 10 So this is another very complicating factor.
 11 In this study, they also looked at even higher
 12 efficacy opioids than the ones I'm showing you
 13 here. They compared the effects of hydromorphone,
 14 fentanyl, and sufentanil, and this relationship
 15 differs for those drugs as well.
 16 Another thing that we've kind of touched on
 17 in the last couple of days is the level of physical
 18 dependence and how that impacts on calculations of
 19 relative potency. What I'm showing you here are
 20 data from a study that was collected in rats using
 21 a radiant heat tail-flick assay.
 22 What they did was, in the top panel, they're

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1 examining the anti-nociceptive effects of morphine
2 under controlled conditions where they're not
3 physically dependent, and then in the closed
4 symbols, they made the animals physically
5 dependent. They provided a constant infusion of
6 morphine for 7 days, and then they tested the
7 analgesic effects of morphine under those
8 conditions.

9 The top panel shows the low maintenance dose
10 of morphine, the middle shows the intermediate
11 maintenance dose, and the bottom panel shows the
12 high maintenance dose of morphine. You can see
13 with the increasing maintenance doses, it shifts to
14 the right in the dose-response curve. But this
15 relationship varies depending on the agonist that's
16 tested.

17 These are all dose-effect curves that were
18 conducted under both pre-morphine and post-morphine
19 maintenance. So morphine, as I showed you in the
20 upper-left corner, is showing a rightward shift,
21 but fentanyl to the right of that shows no shift in
22 the dose-response curve. Meperidine shows a modest

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1 shift as well. On the bottom panel, to the very
2 left, is methadone; the next one is buprenorphine;
3 and the one next to that is the etorphine.
4 Methadone and etorphine also showed no shift to the
5 right in the dose-response curve. Buprenorphine
6 obviously showed the shift downward, and then
7 levorphanol shows a shift to the right. So the
8 impact of the physical dependence is an important
9 variable, as is the agonist that's tested.

10 Then, on top of that, the opioid that is
11 used to generate the physical dependence is also
12 really critical because when they made animals
13 physically dependent on fentanyl, rather than
14 morphine -- so they provided a constant 7-day
15 infusion of fentanyl -- these rightward shifts
16 disappeared.

17 This is really under the best experimental
18 conditions where you have total control of all of
19 these kinds of parameters, same strain of animals,
20 same conditions, same experimenter, and you get
21 these really dramatic increases and differences in
22 effect. Other variables that I'm not going to go

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1 into include sex differences, genetic differences,
2 so it's no wonder that we're having this meeting
3 today, actually.

4 Then the last but not least, the methods of
5 assessing the endpoints also can be different.
6 There's the observational method to look at
7 clinical responses and try to match the doses of
8 the different drugs that you're testing. There's
9 the experimental method that I was just describing
10 looking at rank order of potency and looking at
11 ED50 values. Shanna described the Finney assay as
12 the statistical method of making potency
13 comparisons.

14 There are all kinds of others.
15 Dr. McPherson described some of them yesterday, and
16 I think a couple of the other speakers did as well.
17 So I think this is one of the questions that we're
18 going to try to answer today, which method is best?
19 So, thank you.

20 DR. CHAI: Thank you, Dr. Comer, and thank
21 you for bringing up so many interesting insights
22 for us to discuss this afternoon. I'm looking

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1 forward to a really robust discussion today.

2 For our last presentation of this fantastic
3 workshop, we have Dr. Nabarun Dasgupta, who will be
4 presenting some very interesting findings from a
5 recently conducted study on interpretation of
6 morphine equivalents with a focus on calculations
7 of MMEs.

8 Thank you, Dr. Dasgupta. Just so that you
9 know, I know you have a lot of slides, if you need
10 a little bit of time, we can try to find a few
11 minutes for you. So please take your time; not too
12 long of course, but if you need a little bit of
13 time, we'll find it for you. Thank you.

14 DR. DASGUPTA: Thanks, Dr. Chai. I should
15 be able to get through it.

16 Presentation – Nabarun Dasgupta

17 DR. DASGUPTA: What if we have unwittingly
18 been calculating daily MMEs in different ways, but
19 never realized it, independent of the conversion
20 tables?

21 Fifteen years ago. I published the first
22 paper to use MME in an epidemiology study, but I've

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1 had a hard time convincing colleagues that subtle
2 choices have big consequences since then. So we
3 initiated this research to set things straight.
4 Today, I'm going to show you something that
5 once you see it, you can never unsee it, something
6 that will fundamentally change how you view daily
7 MME and a 90-MME per day threshold. This study was
8 funded by FDA and the Department of Justice, but
9 the views are not necessarily endorsed by these
10 agencies. Maybe they will be someday.
11 The materials in this analysis are also
12 freely available, and we're giving universal
13 permission for reuse. The details are all
14 available at go.unc.edu/mme, and the paper has been
15 accepted at Clinical Journal of Pain and should be
16 available in a couple weeks.
17 We've also translated all the SAS code,
18 Python code, and data [indiscernible] code to help
19 others using these metrics. We'll get bar code up
20 there soon. And as I speak, the slides should
21 appear on Twitter. We're doing a little bit of
22 experiment with links to papers and additional

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1 resources. We'll see how that goes.
2 So far in this workshop, we have heard a lot
3 about how conversion factors are imperfect. The
4 purpose of this presentation is to show you
5 something new. We reveal that there are more even
6 more fundamental and more influential issues with
7 daily MME calculation than conversion factors and
8 pharmacology alone.
9 The problem is that there are actually four
10 different ways to calculate MME per day, but these
11 differences have been entirely overlooked. The
12 solution we offer is a clear understanding of how
13 to calculate daily MME and how to choose between
14 the different definitions.
15 The daily MME has been enshrined into law in
16 14 states, which make the assumption that daily MME
17 is a standardized clinical metric. The MME is not
18 a standardized clinical metric. None of the laws
19 define how to calculate MME per day because they
20 assume that it is a clinically standardized metric.
21 To start with, let's imagine that we give
22 four analysts the same data and ask them to

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1 identify which are the, quote/unquote, "high-dose
2 opioid analgesic" patients; same time period; same
3 location; same patient; same prescription; same
4 identical data set. We can even specify which
5 conversion factors to use and tell them to use
6 90 MME per day to define high dose. And then we
7 can tell them to only use daily MME definitions
8 that were vetted by and cited in the CDC guideline.
9 It sounds like a pretty boring experiment, right?
10 Well, this is how it plays out. Each of the
11 four analysts identify a different set of patients
12 who are high dose. They agree at the extreme top
13 and bottom of the range, but in the space where
14 most long-term patients fall, there was simply no
15 consensus. What happened? How is there any room
16 for variability here? They were using the same
17 conversion factors. So something beyond
18 pharmacology is happening here.
19 To get to the root of the problem, let's
20 give the same four analysts a simple scenario.
21 Here is a patient with two prescriptions. Both
22 prescriptions are dispensed on the first day of a

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1 30-day month. We modified this example that
2 appears in the CDC CME training module by adding
3 one more script. If you're following along at
4 home, you may want to screencap this slide. I
5 promise this won't be more complicated than basic
6 arithmetic.
7 The first script is 30-mg ER oxycodone twice
8 a day for around-the-clock pain for 30 days, so
9 we're looking at 60 tablets which have 2700 mg MME,
10 assuming a 1.5 conversion factor. For the second
11 script, it's one 5-mg oxycodone twice a day as
12 needed for breakthrough pain for the first 7 days,
13 105 mgs, for a total of 2805 MME between the
14 scripts. So you might want to jot down 2805
15 because you'll see that number again in a moment.
16 Four analysts would actually disagree on how
17 much daily MME this patient is getting. Their
18 calculations will range from 35 to 105 MME. Half
19 are saying that this is a high-dose patient, the
20 other half are saying they're not. This same thing
21 could happen across doctors within the same
22 clinical practice if their definitions aren't

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1 standardized or between a prescriber and an
2 insurance company,
3 So far in this workshop, we've concentrated
4 on the MME part of MME per day; the numerator is
5 what we've concentrated on. What we haven't
6 considered is the denominator, a day. To borrow a
7 line from the musical, Rent, how do we measure a
8 day in the life of a patient? I'll spare you for
9 not singing the chorus, but you get the picture.
10 Next, I'll show you how these four measures
11 were derived. We took a careful look at all of the
12 studies cited in the CDC guideline to justify the
13 90 MME threshold. Of these, we found 18 that used
14 daily MME. We combed over the methods and
15 appendices and reverse-engineered the underlying
16 equations, which none of the papers explicitly
17 included. Look, my own paper is on here, and I am
18 just as guilty as everyone else, and I apologize.
19 So this is something I'm doing here today to
20 rectify some of my own past mistakes.
21 In the accepted paper accompanying this
22 presentation, we reproduced the verbatim extracts

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1 from each of these 18 papers, some of which I'll
2 show you in just a moment. I know it's a little
3 hard to believe, but the 18 studies used to
4 establish the threshold silently used four
5 different definitions. In some cases, the same
6 authors used different definitions between studies
7 without any comment. So this possibly can't be a
8 big deal, right? Well, let's find out.
9 To atone for the lack of detail in my own
10 published studies, I worked with Alan Kinlaw to
11 reverse-engineer these equations. At its heart,
12 the four definitions are measuring different
13 things. What we are building to here is that
14 90 MME is not a standardized clinical metric. We
15 face this challenge in other parts of medicine like
16 with prostate-specific antigen tests, but we
17 haven't even noticed that it's happening in pain
18 medicine.
19 Next, I'm going to show you some equations,
20 but if you don't speak scientific Greek, that's ok;
21 just focus on the numbers. This slide is here for
22 completeness. We've heard lots of brilliant

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1 discussion about the pharmacology, but that's not
2 something that most patients, and even most
3 doctors, feel comfortable challenging. In
4 contrast, what I'm about to show you is nothing
5 more than basic arithmetic. You can do this at
6 home. I think Dr. McPherson said it best yesterday
7 when she said, "Call a third grader."
8 Ready? We're going to briskly walk through
9 and see how these equations apply to that
10 two-prescription scenario you saw earlier.
11 The first definition we call total days'
12 supply. In this definition, the numerator is 2805
13 that you saw earlier, the denominator is 37 days,
14 adding up the days' supply for the two
15 prescriptions, 30 and 7. Dividing these numbers,
16 we get 75.8 daily MME.
17 This is the most common definition used in
18 the literature, and this paper by Von Korff is the
19 one that's by far the most commonly cited for
20 definitions. Dr. Zhang yesterday pointed out that
21 this was also cited in the printed CDC guideline,
22 conferring with it de facto credibility, and this

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1 is the metric that often shows up in clinical data
2 dashboards, including PDMPs.
3 Two things to note: first, the days' supply
4 can exceed calendar days; that's weird; second,
5 this definition is perverse. By adding a second
6 script for breakthrough, you actually get a lower
7 daily MME. On a clinical basis, this measure
8 doesn't make a lot of sense at all, but on a
9 population level, I see this citation and measure
10 use all the time, in part, because it's so easy to
11 calculate on a large scale.
12 The next definition is similar but takes
13 into account overlapping days, so the denominator
14 is 30 calendar days. Dividing, we get
15 93.5 daily MME. Just with this subtle change in
16 denominator, we end up on the other side of the
17 90 MME threshold. This probably makes sense to
18 most clinicians, but it was only used in 2 out of
19 18 studies cited in the CDC guideline. This is
20 also the method that the HHS Office of the
21 Inspector General recommends, and they provide a
22 handy set of tools to calculate it in SAS, R, and

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1 SQL.

2 The third definition uses a fixed number of

3 days for the denominator. Clinicians may be

4 baffled, but this is actually the method that's

5 used in a lot of papers in the CDC guideline and

6 the single most cited paper on the risk of dose and

7 overdose mortality, which is this paper by Kate

8 Dunn. This definition has also been used in CDC

9 published studies.

10 Going back to 2805 for the numerator, when

11 we put 90 days in the denominator, we get

12 31.2 daily MME. This method gets used a lot in

13 research, but it's unclear if those findings would

14 have clinical relevance. In the studies cited in

15 the guideline, 90 days was most common, but some

16 studies use longer periods of time, up to 365 days,

17 further shrinking the daily MME. And inpatient

18 Medicare studies often use 13 days because that's

19 the reimbursement cliff. We went with 90 because

20 that is the most common.

21 Finally, the fourth definition, D4, is

22 something we call maximum daily dose. This is the

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1 definition used in the mobile app for clinicians

2 that accompany the CDC guideline. They call this

3 the total daily dose in their publication, but we

4 think maximum is a better word because it reflects

5 the equation better.

6 This definition ignores days' supply and

7 dates for the prescriptions. It assumes the

8 maximum dose on one day, ignoring intentional

9 self-harm. Using this definition, 90 MME plus 15

10 gives us 105. Not surprisingly, as you'll see, max

11 daily dose returns the highest measurement.

12 This definition is actually a bit tricky to

13 implement with staggered start overlapping scripts,

14 but we have shared our code to help. It's worth

15 noting that this definition is different from the

16 one suggested by HHS Office of the Inspector

17 General, so here we have two federal agencies

18 saying different things on how to calculate this

19 very essential metric.

20 One of the analysts on our team, Yanning,

21 works with software engineers who process PDMP data

22 and other large data sets. She's been frustrated

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1 that most software vendors won't even give you

2 enough detail to know how MME per day was

3 calculated, let alone explain it in terms for

4 clinical decision making.

5 This is a real-world problem, guys, a

6 practical problem that impacts clinical decision,

7 data, and tools, and really calls into question the

8 evidence base that underlies some of our

9 fundamental understanding.

10 So we established that there are four ways

11 to calculate daily MME. But, hey, is this all just

12 academic? Fair question. So let me show you.

13 We did a controlled experiment. Imagine we

14 have two places, and we observed that one place has

15 a higher opioid prescribing rate than the other,

16 8.7 versus 7.9 per hundred adults. This is exactly

17 the setup used in a lot of policy and intervention

18 evaluations in epidemiology research. For our

19 purposes, the cause of the difference is less

20 important. Let's just agree that a difference

21 exists and that we want to measure it.

22 Given the mild imbalance of rates on this

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1 slide, we may want to know a little bit more, like

2 if there is a difference in the proportion of

3 high-dose patients between these two places, so we

4 did a study comparing two locations like we would

5 in a policy intervention analysis.

6 We conceptualized this as if these were four

7 different papers using the same exact data set,

8 evaluating the same exact intervention or policy.

9 The key thing to remember here is that the only

10 source of variation -- the only source of

11 variation -- comes from the four definitions.

12 Here are the methods. We used outpatient

13 dispensing data from PDMPs in California and

14 Florida. We chose a short 3-month period to avoid

15 secular time trends. We defined high dose as

16 greater than 90 MME, and we looked at solid oral

17 and transdermal opioids -- opioid analgesics.

18 Actually, it should have been mentioned on the

19 slide; my apologies.

20 We used a CDC conversion table as

21 equianalgesic potency. Equations allow you to

22 substitute other potency factors, but we held them

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1 constant here because we're focused on the
2 denominator.
3 For statistical analysis, we did three main
4 things. First, we compared the percent of
5 high-dose patients between Florida and California,
6 varying only the definition of daily MME. Second,
7 we quantified the milligram difference in average
8 opioid dose per day, varying only the definition of
9 daily MME.
10 Third, we conducted a meta-analysis seeing
11 if four different studies using the same data set
12 and the same conversion factors would have
13 statistically agreed with each other. This method
14 is used a lot in observational studies and clinical
15 trials to evaluate if a set of studies are even
16 comparable, if they measure the same thing. This
17 was a method that we applied, that we borrowed from
18 colleagues at FDA who presented something similar
19 at an ADCOM last year. Thanks guys.
20 For sample size, we have about 9.5 million
21 prescriptions representing about 4 million
22 patients. The numbers you saw earlier were real.

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1 Here's the 3-month dispensing rates for California
2 and Florida in the third quarter of 2018. We chose
3 these places because these are two of the three
4 most populous states in the country, and for good
5 measure, I'll show you preliminary data from Texas
6 as well.
7 Here are the California results first; same
8 data, same conversion factors, but definitions D1
9 and D4, which are both used in clinical practice,
10 show a 3-fold difference in who was perceived to be
11 high dose.
12 Adding in the Florida results, we see a
13 similar story, with D4 really identifying a lot
14 more high-dose patients than the other three
15 definitions. Remember, the clinicians who might be
16 skeptical about the fixed 90-day denominator,
17 definition 3, well, guess what? D1 and D3 are
18 actually pretty similar.
19 It's worth pointing out that the definitions
20 perform differently in each state. While D3
21 returned the fewest high-dose patients in
22 California, it was D1 that was the lowest in

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1 Florida.
2 We also have preliminary data from the Texas
3 PDMP for the first quarter of 2020 at the outset of
4 the pandemic. You can see a similar pattern across
5 the four definitions, but the overall proportions
6 are lower. This could be due to time trends, but
7 also that Texas tends to prefer IR hydrocodone way
8 more than other places. But the takeaway here is
9 across the three largest states in the country,
10 these definitions disagree whether hundreds of
11 thousands of patients are high dose or not.
12 Taking the same data, if we were doing a
13 policy or intervention analysis comparing the two
14 places, the four studies on the same data set
15 wouldn't even come close to agreeing. Was there
16 39 percent more high-dose patients in Florida or
17 was it 84 percent?
18 Those are big, big differences in terms of
19 policy interpretation. In fact, the heterogeneity
20 from definition alone is so high that we wouldn't
21 be able to combine these into summary measures in a
22 meta-analysis. This really calls into question a

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1 lot of what's published in the scientific
2 literature, in epidemiology studies, at least.
3 Instead of percents, we may want to know how
4 much higher doses were given in one place versus
5 another. The four definitions don't even agree if
6 the average ER-only pain patient is getting a high
7 dose. We're going to look at those data a little
8 bit more carefully here.
9 We are still comparing milligram differences
10 between Florida and California. The vertical axis
11 is average MME per day. Each blue bar is a
12 different definition. The way to read this chart
13 is that the bottom of the bar is California and the
14 top is Florida; Florida is always higher. The
15 height of the bar is how different the states are
16 in terms of average milligrams of MME. Using
17 maximum daily dose D4, you get a really big
18 difference, but these numbers are really all over
19 the place.
20 Alright. Ready? It gets worse. The means
21 were highly right-skewed, meaning ultra high-dose
22 outliers were driving averages to be unnaturally

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1 high. In these situations, we turn to medians, in
2 orange, as some of the published studies do as
3 well. Here are where things get even more
4 interesting.

5 Alright. Whoever's touching the slides
6 among the other speakers, please lay off.

7 D4, which exaggerated the differences
8 between states using the arithmetic average
9 actually returns much less variation between states
10 in the median. D3 median shows the least
11 difference at 0.9 mgs. The message here is that
12 subtle choices have major consequences for policy
13 and intervention evaluation.

14 But which one of these is correct? I
15 honestly don't know. It depends on the research
16 question is their usual answer. But it's not as
17 simple as choosing something in the middle, so
18 that's our natural cognitive tendency.

19 Each bar on this plot could legitimately
20 have been justified in an observational study and
21 glossed over in the method section. It's a mess.
22 While they all point to doses being higher in

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1 Florida, they really call into question what is
2 actually being measured. Policy and intervention
3 studies, even small effects with large data sets,
4 can carry a lot of inferential-related
5 [indiscernible].

6 My recommendation is to let go of the 90 MME
7 threshold and odds ratios that have been using
8 these types of studies and instead treat MME as
9 continuous and use multiple metrics. At the very
10 least, please, please, please state the definition
11 or equation that you're using.

12 How do these definitions impact our
13 interpretation? Well using D3 and medians, you
14 could conclude that there are a lot more high-dose
15 patients in Florida, but they're only getting one
16 milligram more, or you could conclude that there
17 are definitely more high-dose patients in Florida,
18 but on average they're getting a lot, lot more,
19 13 milligrams more. So if you're evaluating an
20 intervention or policy, or you're designing one,
21 these subtle choices have really big consequences
22 in what you're actually observing. When you break

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1 this analysis out by IR and ER, you see lots of
2 heterogeneity, so much so, that a meta-analysis
3 would conclude that these studies were so
4 heterogeneous that you can't combine them to
5 summarize.

6 The other incredible thing here is patient
7 selection. In pharma-sponsored observational
8 studies, you sometimes look at only people who are
9 getting ER opioids to make the cleanest possible
10 comparisons if you're comparing between ER opioids
11 without the additional confounding of breakthrough
12 pain IR opioids.

13 If we did the study on ER-only patients
14 alone, we would actually conclude that California
15 had the higher opioid doses not Florida; again,
16 subtle choices, major consequences.

17 So why is this happening? Despite variation
18 and underlying definitions, the studies cited in
19 the CDC guideline consistently found an increased
20 risk of fatal overdose above 90 MME. The simplest
21 explanation is it is an artifact of turning a
22 continuous metric into one that is categorical.

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1 All but two of the studies cited in the guideline
2 categorized MME exposure using 90 to 120 milligrams
3 as the lower bound for the highest stratum, meaning
4 everything else above 90 or 120 was homogenized.
5 Our study supports FDA's contention that overdose
6 risk with opioid analgesics is actually a
7 continuous function.

8 A big part of the issue here is overlapping
9 scripts. These really impact how the definitions
10 perform. So how common are overlapping scripts?
11 Forty-two percent of prescriptions overlapped with
12 another script in our sample. It affected one out
13 of every four patients, including most long-term
14 patients.

15 Let me address epidemiologists and
16 statisticians in the audience. It may seem that
17 choosing one definition and applying it over time
18 would be less worrisome. In most other countries
19 this is true. However, when you look at the
20 equations carefully, two specific time trend
21 scenarios emerge as problematic in the United
22 States.

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1 First, if overlapping scripts decrease over
2 time, choosing definition 1, total days' supply,
3 will attenuate intervention effects compared to
4 definition 2 differentially at earlier time points.
5 Second, if ER and IR dispensing don't decline at
6 the same rate over time, so non-parallel linearity,
7 this same thing will happen.
8 Both of these prescribing trends happened in
9 the U.S. over the past decade, so the choice of
10 definitions has some special context in this
11 country. We're doing some simulation studies to
12 quantify this, but in preliminary work, the
13 differential effect could be as high as 33 percent
14 of the intervention effect. So the point here is
15 that subtle choices in measurement have major
16 consequences on interpretation of interrupted time
17 series analyses.
18 We also explored what happens at the
19 threshold boundary, comparing 90.0 as a threshold
20 to 90.9. Where precisely do you draw that line for
21 high dose? Published studies often don't make that
22 very clear in the words that they use. If you

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1 shift the high-dose threshold from 90.9 down to
2 90.0, you increase the number of high-dose patients
3 by 15 percent. That means there are a lot of
4 patients who are being held at this artificial
5 threshold despite the definitions not being
6 clinically standardized.
7 June, an analyst on our team, thought this
8 was unexpectedly huge, and I totally agree. He
9 points out that these little changes in studies can
10 lead to misclassification. So we quantified the
11 extent of misclassification.
12 Think of this like a doctor and an insurance
13 company setting the threshold on either side of
14 that very tiny boundary, 90.0 or 90.9, something
15 we'll think of as a rounding error. Using
16 definition 1, the insurance company and the
17 physician would disagree for one out of every
18 56 patients whether the beneficiary was getting a
19 high dose or not. With definition 4, every 1 in
20 30, it's worth noting that definition 3 is the most
21 robust to this kind of discrepancy, so for certain
22 kinds of epi studies, it might have some relevance.

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1 To cover some of the limitations, we've
2 assumed that all medications are taken as directed
3 and we have combined cancer and non-cancer pain
4 looking across the board for opioids. There are
5 plenty of other pharmacological issues that we've
6 talked about already, but because we're not
7 combining this with an outcome measure, we're just
8 kind of doing it as a simulation study, some of
9 these issues are a little bit less relevant.
10 So which definition should we use? Toska
11 from our team had a succinct reply. There's no
12 one-size-fits-all approach, but at the least we
13 need to be showing our work. As a side note, we're
14 doubly proud of Toska for this past week being
15 enrolled in the first class of the U.S. Public
16 Health Service's new reservist program, so
17 congrats, Toska.
18 We've heard lots of reasons for clinical
19 caution using MME, so let me address this in terms
20 of epidemiology and policy intervention evaluation.
21 I don't think D1 should be used, period. D2 is the
22 version I used.

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1 D3 is a more robust misclassification, so if
2 you have messy data, this may be attractive. It
3 also might be really good for long-term studies
4 where there could be gaps between script refills
5 and things like that.
6 D4 could be useful for very short-term
7 toxicity studies in opioid-naïve patients where you
8 don't have a risk of suicide, but definitely not
9 for long-term situations. Its inaccuracy actually
10 grows with time, and you can intuit that from
11 staring at the equation long enough.
12 But candidly, right now if a paper doesn't
13 sufficiently define how they calculate daily MME, I
14 don't read the results. I just can't make sense of
15 it after having done this analysis because these
16 metrics are so fundamentally different.
17 We're also building a research tool to help
18 select metrics. Here's a screencap of the
19 prototype. If you want to be a beta tester, please
20 drop me an email, which you'll see on the last
21 slide. We're going to try to help some decision
22 making from the research, policy, and intervention

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1 evaluation side.

2 In conclusion, let's turn to the folks with
3 lived experience, to the patients and clinicians
4 who actually think these disease definition choices
5 matter. Here's how this plays out in practice with
6 payers.

7 Arkansas Medicaid required beneficiaries
8 with greater than 250 MME per day to be tapered to
9 90 mgs during an 18-month period; yet, we saw how
10 D4 is not ideal for patients already on opioid
11 therapy. But using the CDC mobile app, this could
12 easily be the definition applied here clinically,
13 while another prescriber may choose on-therapy
14 days, say definition 2. The bottom line here is
15 that 90 MME cannot be considered a hard threshold
16 because it is not a standardized clinical metric.

17 Dr. Chidgey, who's one of the panelists here
18 today and an author on the study had this to say.
19 "While payers insist they're not dictating care
20 because the patient can still pay out of pocket for
21 the medication" -- I have many who do -- "for most
22 patients, this is not financially feasible." She

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1 also emphasizes that proper pain management truly
2 typifies the art of medicine, which we've heard
3 from other speakers over the last 24 hours.

4 We also asked a pain patient representative
5 on our team to weigh in on the analysis you just
6 saw. Liz Joniak Grant, who often is on FDA
7 advisory committees, as well, as the patient
8 representative, says, "Far too often, we are
9 victims of the good intentions of those wanting to
10 do something about the opioid overdose epidemic,
11 but the something that is done oversimplifies the
12 problem and pushes cookbook medicine upon those of
13 us with complicated medical situations. So we
14 wait, and we suffer, and we hope it will get sorted
15 so we can get the care we need."

16 And finally, Chris Delcher, one of our other
17 authors, points out that this work is an example of
18 how we can put PDMP data to work positively for
19 patient care. We acknowledge that a lot of patient
20 experiences with PDMPs might have been negative in
21 the past, but in this case, we worked closely with
22 the state PDMPs for this analysis, and had the

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1 opportunity -- [inaudible -- audio gap] -- to
2 educate them on the impact of these important
3 consequences.

4 Alright. So here's my key message; little
5 choices have big consequences. What we have seen
6 here today, and reinforced by all the
7 presentations, is proof that daily MME is not a
8 standardized clinical metric. For the first time
9 in public, we reveal that simple arithmetic might
10 have a stronger impact on MME-per-day calculation
11 than pharmacology alone.

12 Why has such a measurement failure not been
13 detected sooner? Here's my take. Computational
14 ease and evocative lure of molecular fundamentals
15 collide in an optimal level of cognitive complexity
16 to engender MMEs with an unsubstantiated aura of
17 immutability. They're not immutable.

18 If you are a researcher, please, please,
19 please state your definition. Feel free to reuse
20 our equations, or slides, or code. In this way, we
21 can be allied with patients to reduce the most harm
22 with the best information. Thanks to FDA,

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1 Dr. Chai, and the rest of the team for organizing,
2 and thanks to everybody for sticking around.

3 Clarifying Questions to Speakers

4 DR. CHAI: Thank you, Dr. Dasgupta. I think
5 we can all agree that that was a very enlightening
6 presentation and data-driven analyses to really
7 highlight and show some of the complexities just in
8 what you're referring to as the denominator, but
9 very critical to consider in all the science that
10 we are talking about today. So thank you,
11 Dr. Dasgupta, and I appreciate your synopsis at the
12 end. Thank you.

13 So what we'll do now is open the floor to
14 our panel of invited speakers and panelists for
15 clarifying questions for this session's speakers.
16 Please note, we will break for lunch at 12:30, and
17 if there are additional clarifying questions for
18 our speakers, please jot them down. We will try to
19 take additional clarifying questions after lunch,
20 if we can.

21 As a reminder, please use the raised-hand
22 icon to indicate when you have a question, and

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1 please remember to state your name before you speak
2 after I acknowledge you so that we can have an
3 organized session. And please direct your question
4 to a specific presenter, if you can. Please also
5 remember to clear your icon once you have stated
6 your question.
7 If you have a specific slide to be
8 displayed, we will try our best to get you to that
9 slide, if possible. Finally, it would be helpful
10 to acknowledge the end of your question with a
11 thank you or, "That is all for my questions," so
12 that we may move on to the next presenter.
13 My apologies again, but we will only be
14 taking questions from the invited panel of speakers
15 and panelists. We are unable to take questions
16 from the audience.
17 (Pause.)
18 DR. CHAI: We may have lost some speakers.
19 Dr. Parkinson, could you please state your
20 name and your question, as well? Thank you.
21 DR. PARKINSON: Hello. This is Nicola
22 Parkinson from the MHRA. It's just a very quick

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1 question for Dr. Babalonis.
2 DR. CHAI: What did --
3 DR. PARKINSON: Sorry?
4 DR. CHAI: Dr. Babalonis, you said?
5 DR. PARKINSON: Yes, that's correct.
6 You were talking about the oral availability
7 and the IV availability, and the effect of abuse
8 and the potency between morphine -- sorry, the
9 oxycodone and the oxymorphone coding and about
10 bioavailability.
11 But those studies are actually in a very
12 small number of patients, especially with regards
13 to the oral study. I mean, are those results
14 really specific to that particular patient
15 population? Do you think it's going to be the same
16 for a wider population? Thank you.
17 DR. BABALONIS: Sure. That's a really
18 interesting and important question. The data from
19 the oral study and IV study show pretty tight
20 results across participants. I will acknowledge
21 that it was a quite small sample size; it wasn't a
22 population study. So we would need to collect more

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1 population-level data to be able to really
2 interpret the bioavailability.
3 But I think the key outcome that we were
4 trying to show for that study is that whenever you
5 look at abuse potential measures, they are not the
6 same as, say, analgesic measures or physiological
7 measures, such as respiratory depression and pupil
8 diameter. So it's possible that those results
9 would translate to a wider population, but we would
10 have to do those studies to really determine that.
11 But the data within those groups was
12 within-subject, so all participants received
13 placebo in every dose of all the conditions, and
14 the data pretty tightly adhered to each other, so
15 there wasn't a lot of variability between the
16 subjects. Thank you.
17 DR. PARKINSON: Yes. Thank you very much.
18 I think your data was actually quite clear, the
19 data which you had. It just goes to show, really,
20 that the MME calculation and the potency
21 calculations are really very difficult, especially
22 as to how it's actually being administered between

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1 patients. So thank you very much.
2 DR. BABALONIS: Thank you. I appreciate
3 your comment.
4 DR. CHAI: Thank you, Dr. Parkinson and
5 Dr. Babalonis.
6 Are there other clarifying questions for
7 this session?
8 I understand there's been a lot of material
9 presented. What we can also do is try to address
10 other clarifying questions that you may have
11 regarding other presentations that have taken place
12 over the last two days. I understand that a few of
13 our presenters aren't able to join us today, but
14 representatives are available to address any of the
15 presentations, or we can try to address any of the
16 presentations.
17 (No response.)
18 DR. CHAI: I think there's too much to
19 digest, and maybe many of us are also hungry.
20 So what we can do now is break for lunch.
21 Please, if you do have questions, jot them down.
22 What we'll do is come back at 1:20, so please plan

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1 on coming back at 1:20 to begin our second half of
2 day 2 for the panel discussions.
3 At this time, I'd like to welcome Dr. Judy
4 Staffa and Dr. Jennifer Nadel, who will be
5 moderating this afternoon session. So they will be
6 taking over at 1:20. See you back then. Thank
7 you.
8 (Whereupon, at 12:21 p.m., a lunch recess
9 was taken.)
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1 which we are very pumped about because of all of
2 the information we've heard the last couple of
3 days. But the real challenge here is going to be
4 how we are going to pull this all together and
5 actually try to answer some questions that we've
6 tried to draw up, which I'll walk through.
7 Our goal here is -- inasmuch as it's really
8 important to talk about these issues, and we're
9 really happy that everyone has come together and
10 shared some of the work that they've done -- we
11 really want to try, as best we can, to come out of
12 this and go back to the shop and try to build a
13 research agenda.
14 That's really our goal, is to work with our
15 federal partners, determine what are the important
16 priorities in the science in this space, and then
17 figure out how we can do our part to try to help
18 support and generate new knowledge that will make
19 MMEs, their calculation and their application, as
20 meaningful and as productive and helpful to the
21 whole situation of pain management, as well as the
22 opioid crisis, if possible.

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1 AFTERNOON SESSION
2 (1:22 p.m.)
3 DR. CHAI: Welcome back, and I hope you had
4 a nice lunch. We've had a really great group of
5 presentations over the last two days, and I'm just
6 very excited to introduce our next session, as well
7 as our moderators.
8 I'd like to welcome Dr. Judy Staffa and
9 Dr. Jennifer Nadel, who will be moderating our
10 panel discussion question session. Thank you.
11 Panel Discussion
12 DR. STAFFA: Hi. Good afternoon. I'm Judy
13 Staffa. I'm in the Office of Surveillance and
14 Epidemiology, and I'm happy to be helping out with
15 this meeting.
16 Jen, did you want to introduce yourself?
17 DR. NADEL: Hi. This is Jen Nadel. I'm a
18 medical officer in the Division of Anesthesiology,
19 Addiction Medicine, and Pain Medicine.
20 DR. STAFFA: Great.
21 Jen and I are going to tag team on this. We
22 have the privilege of facilitating a discussion,

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1 So with that in mind, I'm going to be trying
2 to facilitate the discussion by calling on folks
3 and making sure everyone is heard as we walk
4 through the questions.
5 Jen has the unenviable task of trying to do
6 her best to record and capture a lot of the themes
7 and the points made, and to try to put them into
8 different buckets the best she can. So she'll be
9 coming in and out of the discussion, needing to
10 clarify or to hear more about certain points. So
11 you'll definitely be hearing from both of us.
12 So to start, I know that the discussion
13 questions were circulated. I'm hoping folks had a
14 chance to look at them prior to the presentations
15 so that you could be thinking about what are the
16 main points that you might want to bring up.
17 But what I wanted to do is walk through them
18 just to give you an idea of what the questions are
19 going to be, so that you can kind of plan your
20 comments, and then we'll go back and start at the
21 beginning and go through the questions one at a
22 time; although I will apologize in advance.

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1 We tried our best to carve these out into
2 completely separate and non-overlapping buckets.
3 And yes, I hear you laughing. It was not possible
4 to do that. This is so complex that all of these
5 areas are overlapping. So we do understand that
6 some of these questions may bleed into others, but
7 there are definite foci for some of these questions
8 that I want to make sure you understand.
9 Just starting to go through them very
10 briefly, in question 1, we really want to start
11 drilling down. We know that in the different
12 application areas of MMEs there may be different
13 knowledge gaps, but there may also be some
14 knowledge gaps that are common to all applications.
15 We want to discuss and go through them kind
16 of in buckets that focus first on considerations
17 relating to the drugs themselves, and then move on
18 to some of the patient-level factors and
19 information where there might be knowledge gaps,
20 and then be thinking about some of the more
21 population-level gaps that we've heard about, as
22 MMEs are used not just in a patient conversion

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1 setting, but in more of a public health or
2 surveillance setting.
3 The second question we want to zoom in on is
4 we're not really asking for specific study designs,
5 but more what types of studies do you see. You've
6 heard some nonclinical work, you've heard clinical
7 work, you've heard claims-based studies; so to give
8 us some ideas of these different areas and what do
9 you see as the kinds of work where we really should
10 be focusing on to get some of the crucial answers
11 in those spaces. So your ideas on that front will
12 be helpful.
13 Then question 3, we want to make sure that
14 these buckets we've identified in question 1, we
15 want to make sure that we haven't missed anything;
16 so other things that perhaps we haven't focused on
17 or we just haven't thought to include or invite
18 people to present about. So we want to make sure
19 we're not missing anything.
20 Then we'll roll into questions 4 and 5, and
21 really get more into the conversion tables
22 themselves and what kind of work do people see.

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1 What are some of the goals of conversion tables?
2 Should there be one common conversion table? Are
3 there certain issues relating to the calculations
4 themselves around conversion where we could target,
5 and to try to figure out where should we be heading
6 in this area that would be the most helpful. So
7 that's questions 4 and 5.
8 Question 6 is, again, other areas that we
9 want to make sure that we haven't missed anything.
10 And I know in some of the clarifying questions
11 yesterday, a couple folks snuck in some different
12 paradigms or different ways to think about this, so
13 that might actually fall nicely under question 6.
14 Then finally in 7, I'm thinking we're going
15 to have a rich discussion. We're going to identify
16 a lot of issues, and then in 7, we're really going
17 to ask people to be thinking about how to
18 prioritize; if this was up to you, what do you
19 think are the most important areas to target first?
20 I know I've come away from these last two
21 days with a new appreciation of even more
22 complexities than I even thought of before. So it

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1 will be helpful for us, as we develop this research
2 agenda, to actually be able to zoom in and
3 prioritize on areas just to get things started.
4 So with that in mind, I wanted to make sure
5 we all understood the ground rules. We're going to
6 do what we did before, which is, if you would like
7 to make a comment, raise your hand. Paul Tran will
8 be keeping track of the folks in the order in which
9 they raise their hand, and I'll call on folks.
10 When I recognize you, if you can unmute
11 yourself and state your name for the record, that
12 will make it easier for the transcriptionist, and
13 then state your comment, and then if you could mute
14 yourself again. And again, if there's a
15 back-and-forth discussion, obviously we'll call on
16 you again.
17 I wanted to also remind you to put your hand
18 down if you've already contributed your thoughts,
19 but feel free to raise your hand again if you have
20 another thought. Then I wanted to just remind my
21 FDA colleagues that are on the panel, if you also
22 have questions or clarifications you'd like to

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1 hear, if you'd like to hear more if someone's made
2 a comment, or you're not really following it, or
3 you want to add to it, by all means raise your hand
4 or chime in on the chat, and I'll know that you
5 want to contribute to the discussion as well.
6 So with that in mind, Jen, anything you
7 wanted to add? Anything I've left out in terms of
8 housekeeping?
9 DR. NADEL: No. I think that you nailed it
10 and got everything we wanted out there to start.
11 DR. STAFFA: Great. Okay.
12 So we're going to start with question 1.
13 And again, I know it's broad, but it's deliberately
14 broad because we want to get the conversation
15 started.
16 Number one is to discuss any potential
17 knowledge gaps in the science that underlie MMEs
18 across various applications. What we were hoping
19 is to take the approach of these three different
20 areas of the considerations with regard to
21 different drugs or different opioid; considerations
22 with regard to different patient-level factors or

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1 gaps in the area, again, of any application,
2 whether it's for conversion, or rotation, or
3 whether it's being used as a risk predictor, or
4 other areas.
5 Then again, in terms of a population level,
6 you've heard a lot of conversations about how MMEs
7 are used not just for individual patients but in
8 populations of patients using claims data to try to
9 identify patients that might be at risk and helping
10 us identify. We'd like to come up with just a list
11 in these different areas of what you think the
12 important gaps are.
13 So I will stop there and see if anybody
14 would like to get the conversation going, in any of
15 these three areas.
16 Dr. Fine?
17 DR. FINE: Great. Well, thank you. Can you
18 hear me alright?
19 DR. STAFFA: Yes, we sure can.
20 DR. FINE: Great. Alrighty.
21 Well, once again this is Perry Fine
22 reporting in from the beautiful Wasatch Front here

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1 in Salt Lake City, Utah. It's really been a joy to
2 hear some of the in-depth presentations the last
3 few days, and I'm so grateful that the FDA is
4 attacking, if you will, this problem yet again.
5 To get to some of these questions I
6 thought -- and really to get the discussion started
7 and not to dominate things at all, but just to
8 create some additional context, there were a few
9 things that were not covered, at least, or maybe
10 glossed over -- to create some context that we can
11 then maybe pinpoint more specific issues around
12 these questions; so if you just give me about a
13 minute here to maybe create some of that context.
14 First, this is not a new problem, and
15 anybody who's been in the field for maybe at least
16 a decade, and longer, knows that this is not the
17 first time that this issue has come up with regards
18 to issues around equianalgesic dose conversion and
19 opioid rotation, et cetera.
20 It's just that we have really not made much
21 progress, and I think some of the questions and
22 some of the comments maybe I made yesterday sort of

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1 point to a little bit of that sense of impatience
2 and frustration with some of the false starts we've
3 made, and that I believe and hope that this time
4 around we can make some better progress.
5 From the historical standpoint, which is not
6 just mere history but has created the foundation
7 for all of what, unfortunately, I believe flawed
8 science -- in other words, a science that has not
9 been built up on a solid foundation of studies that
10 really support the way MMEs have developed and all
11 the issues that have been brought out, is to recall
12 Dr. Ray Hood and others, dating back 30, 40,
13 50 years, and actually the methodology that was
14 used to try and understand at least analgesic
15 equivalency, which was really the issue, was based
16 upon a basic two-dose, crossover methodology,
17 extrapolating then dose conversion based upon an
18 analgesic equivalency, including different routes
19 of administration.
20 Built upon that data, which was very good
21 and very sound, it did not apply to the broader and
22 the typical clinical conditions where opioid

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1 rotation, opioid conversion, and opioid
2 switching -- however we want to term it -- is
3 actually necessary in real-life circumstances.
4 We're not talking exclusively about acute pain, or
5 a single dose, a trauma, or a surgical model, or an
6 animal model. We're talking about protracted use
7 of analgesics and all the variables that therein
8 lie.
9 So if you've built a house on a faulty
10 foundation, you're not going to end up with a very
11 sturdy house, and I think that's where we find
12 ourselves. And I just wanted to summarize that as
13 coming out from what I heard loud and clearly as
14 conclusory points from the presenters that did an
15 exemplary job of pointing out all the flaws and
16 translating acute and experimental pain models of
17 opioid comparative potency to broader clinical
18 application.
19 Lastly, I think it goes without saying,
20 except it needs to be said over and over, that
21 there is a true dearth of prospective trials, in
22 most circumstances, that apply to dose equivalency,

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1 or potency, or dose conversion, in most of the
2 clinical conditions in which we need to apply them,
3 in order to provide not only therapeutic efficacy
4 but safety for patients.
5 With that as a pretty broad context around
6 some of this discussion, with regards to the first
7 question on the drug considerations, I think it's
8 been pointed out -- and I will just repeat
9 it -- that when we go across opioid subtypes from
10 pure agonists to the various other types of opioids
11 that are now in common use, including partial
12 agonists and mixed-effect agonists -- that is,
13 norepinephrine, uptake inhibition, and so forth;
14 methadone with an NMDA receptor phenomenology -- to
15 try and impute or generalize from the limited data
16 that exist, even amongst the agonists, is a leap
17 and, unfortunately leads to faulty conclusions and
18 problems.
19 How we deal with that I'm sure we'll be
20 discussing later on. But I just wanted to
21 emphasize that for discussion point 1A. Thank you.
22 DR. STAFFA: Thank you very much, and thanks

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1 for the background. It's very helpful for folks
2 who may not have been in this space as long as some
3 others, so thank you.
4 Dr. Mellon, did you have a comment to make?
5 Could you unmute yourself and just state your name?
6 DR. MELLON: Certainly. This is Dan Mellon,
7 deputy director for pharmacology and toxicology for
8 the Office of Neuroscience.
9 As a pharmacologist, I thought it would help
10 to perhaps chime in before we start getting into
11 the patient-level aspects that I will clearly defer
12 to my clinical colleagues' expertise on. But one
13 of the things that I was trying to bring out in the
14 presentation today was that there really is a lot
15 that we just don't know about a lot of these older
16 drugs.
17 I think the point that Dr. Fine is making,
18 that the ones that seem to cause the most challenge
19 when it comes to trying to compare these are the
20 ones that have mixed pharmacological profiles -- a
21 little bit of serotonin, a little bit of
22 norepinephrine, activity in NMDA -- we know NMDA

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1 involvement is clearly impacting the degree of
2 tolerance that can show up with these particular
3 compounds, and that can really confound the ability
4 to compare these products.
5 One of the things I think is worth stressing
6 is that we really don't have a great understanding
7 of the profile, even within the opioid receptor
8 class, for what many of these older products
9 actually bind to.
10 In a new drug development program, we would
11 not only get very good opioid receptor binding
12 profile and functional data, but we also get a
13 secondary pharmacological screen, and that
14 secondary pharmacological screen can include 60 to
15 120 different receptors, generally for compounds of
16 this nature, that would be receptors that are
17 located in the central nervous system that very
18 well may help us understand some of the subtle
19 nuances that may be taking place when these
20 products are administered.
21 As pharmacologists and toxicologists, we
22 leverage that data to try to interpret side effects

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1 that don't quite look like what we would expect
2 when we look at toxicology studies or we look at
3 pharmacological studies, but we have very little of
4 that for any of the compounds that we've discussed
5 predominantly today.
6 I think even though it would be very
7 difficult to try to build in and understand the net
8 effect of activation of multiple receptors by these
9 compounds at different doses, the fact that they
10 can alter the way that desensitization can take
11 place, the way that tolerance can develop, I think
12 that's a data gap that really does need to be
13 addressed.
14 I think in the long run, even though at the
15 end of the day, the clinical data are in terms of
16 understanding the risks going to rule and
17 understanding the types of events that were looking
18 at, understanding that pharmacology helps us
19 interpret that data.
20 So I would propose that we actually still
21 miss a great deal of information, basic
22 information, about the drugs that we're discussing

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1 today, and I would hope that at some point we would
2 have an opportunity to build that database and
3 build that foundation of knowledge that hopefully
4 may help contribute to these challenging questions.
5 Thank you.
6 DR. STAFFA: Thanks a lot for that orienting
7 comment. Yes, I think that's very helpful to
8 remember.
9 Dr. Bettinger, I believe you were next.
10 Could you unmute yourself and just state your name?
11 DR. BETTINGER: Absolutely. This is
12 Dr. Jeff Bettinger, pain management, clinical
13 pharmacist up in Saratoga, New York with Saratoga
14 Hospital.
15 I wanted to bring up a couple of points
16 really piggybacking off of what Dr. Fine just
17 brought up and what Dr. Mellon just brought up, I
18 think especially revolving around this first
19 question of any of these potential knowledge gaps
20 regarding utilization of MME and the application.
21 I think the first thing that's essential,
22 and what I think we probably all agree on, is we

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1 need to define in each scenario what the goal is of
2 using the MME calculation. As Dr. Mellon and
3 Dr. Fine were just saying, if the goal is around
4 opioid rotation, for whatever reason -- say someone
5 has developed some tolerance, say there's
6 hyperalgesia, say there are side effects -- then I
7 think a lot of the data that we have is really
8 around the equianalgesic effects of these opioids
9 comparatively.
10 However, that's very different data than
11 what I think has been happening over the past
12 10-plus years, where we started to try to use MME
13 and equate different toxicities and different
14 toxicity profiles between these opioids.
15 The problem is we haven't actually created
16 new data for that. We have in ways, but we haven't
17 studied the equal toxic doses between these
18 different opioids, and it's going to relate to each
19 individual toxicity. So do we want to talk about
20 the abuse liability and the euphoric effects, or do
21 we want to talk about the patient effect, or the
22 respiratory depression effect?

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1 Those doses, because of what Dr. Mellon had
2 just said, and really what his presentation was
3 about, because of the differences in the internal
4 mechanisms between these drugs and these opioids,
5 that's where we can really see some significant
6 differences.
7 So I think that's one part of this that
8 maybe we as a group, or going forward, have to
9 address and figure out what is the goal of the MME
10 calculation. Because I think what we will likely
11 find, if we really start to study this going
12 forward, equianalgesic dose in conversion factors
13 may be very different than equal respiratory
14 depression doses, in effect; again, because there
15 are so many differences in individual
16 characteristics of these opioids.
17 I think that's a huge knowledge gap that
18 we're going to have to address at some point, and
19 that kind of leads me to my next point.
20 I think the other thing we have to look at,
21 especially from a population level, is what are we
22 looking at in terms of the goals of limiting an

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1 opioid if we want to establish from a toxicity
2 perspective and a toxic profile perspective of
3 these opioids and we want to limit them by dose,
4 which we've seen certain states have enacted
5 legislation for this; we've seen third-party payers
6 do the same.

7 It was brought up multiple times between our
8 presenters and again yesterday by the public
9 comment section. States and third-party payers are
10 beginning to limit doses of opioids based off of
11 these MME calculations.

12 One knowledge gap is, what is the impact of
13 doing that in the states that are limiting opioid
14 prescriptions based off of MME? Are their overdose
15 data rates better than states that don't have that
16 limitation? Are their overall addiction, or
17 substance-use, or abuse rates different than that?
18 Which is a little bit more difficult to judge, and
19 all of it's difficult to judge.

20 But I think that's the other big knowledge
21 gap. And again, I may be getting into some of
22 these other discussion questions, too, but I think,

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1 again, it's figuring out what is the goal of
2 limiting an opioid by MME because, again, the
3 studies -- I know we all like to cite the CDC
4 guideline about what they recommend, even though I
5 know Dr. Fine and several others on here were a
6 part of guidelines that took place in 2009, years
7 before the CDC came out, in terms of guidance
8 around chronic opioid use.

9 But around that potential risk of opioid
10 doses greater than 90 that were associated with
11 greater respiratory depression rates and greater
12 substance-abuse rates, what's the real live data
13 going on when we start enacting these cutoffs and
14 these things that states and, again, third-party
15 payers have started to look at? So I think that's
16 another knowledge gap.

17 Then of course, with the individual drugs,
18 as Dr. Mellon just said, buprenorphine, tramadol,
19 tapentadol, methadone, looking at those and, again,
20 individualizing conversion factors that we may have
21 to individualize based off of are we looking at
22 analgesics versus toxic effects.

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1 So a lot there, but I just wanted to throw
2 those out there, too. Thank you.

3 DR. STAFFA: Thank you, Dr. Bettinger.

4 You're really amplifying these particular drugs
5 that we really need to understand more about, as
6 well as the outcomes other than analgesic potency;
7 you mentioned respiratory depression and others, to
8 be developing more of the science there and not to
9 be assuming the differences we see with analgesia
10 that applies to others, and I think we saw examples
11 of that as well.

12 Then I think you also raised this issue of
13 the science around the evaluation of the impact of
14 these, and I think that was tackled head-on in
15 Dr. Dasgupta's talk. So I think that's also
16 science that we can improve. Thank you.

17 Dr. Fine, did you have something else to add
18 on this topic, on this question?

19 DR. FINE: Yes, if I can respond back.

20 First of all, Dr. Bettinger, thank you for
21 underscoring -- and it can't be said enough. Thank
22 you, thank you, thank you for underscoring the fact

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1 that unless there's a specific purpose for which
2 there is a scientific basis for looking at, quote,
3 "MME" per se, there's a high likelihood of creating
4 real problems, which I think is exactly what we've
5 seen.

6 The specificity of purpose or intention is
7 very, very important. Then, of course,
8 generalizing from the data or absence of the data
9 is where we either create good policy, or good
10 principles of practice in guidelines and guidance,
11 or we get into trouble.

12 With that in mind, I want to remind
13 everybody, or at least my understanding of things,
14 that the interpretation of an association of higher
15 doses of opioids leading to greater morbidity and
16 mortality is definitely an association, but is not
17 a correlation.

18 There has not been good correlative science
19 that has gone to the question of why and what's to
20 account for it. In other words, is this a symptom
21 or a sign? Unless we understand the root cause of
22 what's motivating higher dose use in prescription

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1 or less utilization of these drugs by the patient,
2 at the patient level, it's tempting to jump to
3 conclusions, which then were made for all sorts of
4 reasons. But those conclusions can be quite
5 specious and lead to really detrimental outcomes.
6 I think some of the comments made, a lot of the
7 comments made, by the public yesterday afternoon
8 speak to that.

9 Then Dr. Mellon, when you were just
10 speaking, it reminded me that you had underscored
11 the importance of the newer science of
12 understanding pharmacogenetics, and especially
13 splice variants and dimers and so forth. In the
14 absence of understanding at an individual level the
15 effects, drug-specific effects, at genetically
16 developed receptor sites, all bets are off the
17 table.

18 If you go back to work done by Gav Pasternak
19 and some of the knockout mice modeling, Chuck
20 Inturrisi, and others, where this science began, we
21 started to have an understanding of the basis of
22 science underlying incomplete cross-tolerances. So

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1 then, if you started looking at toxicity, it may
2 have nothing whatsoever to do with therapeutic use
3 indications, but they're closely related.

4 From the standpoint of toxicity as we now
5 understand it, especially with regards to opioid
6 switching and incomplete cross-tolerance, unless we
7 can understand this on a personalized basis,
8 there's no chart, graph, table, or app that will
9 give us that kind of information; it's sort of
10 imputed. I know this will probably be a discussion
11 point later on of what do we do about that; we
12 still have to live in this world.

13 But certainly, I think there is adequate
14 data right now - and maybe this can be a question
15 to the group to discuss with regards to patient and
16 population-level stuff. It seems to me that my
17 understanding of the current data, it's the rate of
18 increase as a percent rather than some linear or
19 arbitrary cutoff dose for which there's a
20 relationship with toxicity.

21 Those nonlinear changes at least can provide
22 some guidance for clinicians in the absence of

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1 understanding other contributors of toxicity,
2 including those related to cross-tolerance, and
3 then exposing an individual to risk if they tend to
4 have a more potent agonistic effect than a
5 non-potent effect based upon their genetic profile.

6 So thank you both for introducing those
7 concepts, and I think they make incredibly
8 important discussion points as we move towards
9 potential solutions. Thank you.

10 DR. STAFFA: Thank you, Dr. Fine.
11 Dr. Chidgey, would you like to unmute
12 please, and just state your name and then provide
13 your comment?

14 DR. CHIDGEY: Yes. This is Brooke Chidgey.
15 I totally agree with what has been said, and I
16 think the idea of defining what the goal of the MME
17 is, is essential.

18 I think that's where we have gone astray, as
19 we have many competing interests from the payers,
20 from the medical boards, from law enforcement, and
21 then from patients, all using the MME in a
22 different way in order to advance their agenda in

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1 some way, and obviously in the name of trying to
2 get at a huge problem that our country is facing.
3 But in doing so, there are so many unintended
4 consequences that we are seeing, and that was
5 definitely highlighted in the public comments
6 yesterday.

7 I think the idea of there just aren't great
8 prospective trials is huge, and the idea that
9 correlation does not equal causation, and how easy
10 it is to interpret lack of data as an efficacy; and
11 that's been done a lot when talking about the use
12 of opioids for chronic pain. Then again, just the
13 underlying pharmacogenetic aspect of it I think is
14 huge and really does have an effect on how much of
15 this medicine, the opioid, the patient has actually
16 seen from both side effects, but analgesic
17 benefits. Thank you.

18 DR. STAFFA: Thank you so much
19 Ms. Cowan, did you want to unmute and just
20 state your name and provide your comment?

21 MS. COWAN: Yes. My name is Penney Cowan,
22 and I'm talking from the point of view of the

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1 person living with pain. One of the things I keep
2 hearing is about the MME levels and the reduction
3 of pain, but I think there's more to consider when
4 you're a person living with pain. It's not just
5 about the pain; it's about our quality of life and
6 our ability to function.

7 In these levels, there are so many averages
8 and numbers that come out of all this. I've
9 listened over the last two days, and there are all
10 these charts and apps. And unfortunately, my guess
11 is that most folks probably don't fit into any of
12 those because they're all very individual and
13 different.

14 So I think one of the things that we have to
15 look at is not just the number of MMEs, but also
16 are they able to function and have a quality of
17 life? In other words, can they get out there and
18 be a productive part of society when we look at
19 this MME number? I think that is really critical.

20 I heard about the 14 states, and that
21 bothered me a little bit, only because is it
22 possible instead of doing it -- because I can just

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1 see people going from one state to another and
2 crossing, and that's what happens because it's
3 different in their state, so then they have better
4 access in another state. I know one of the
5 comments that I had in my talk was one of the
6 gentlemen said he would have to commit suicide if
7 he couldn't travel every three months out of state
8 to get his pain medication.

9 I mean, there are a number of human factors
10 that are involved, that while all of the science is
11 great and I am so impressed with all the work
12 that's being done, I'm not hearing some of the
13 other pieces that I think are really critical and
14 important to a person living with pain.

15 It sort of goes back to that balanced
16 approach that we're looking at, at medication, and
17 this is how you manage pain, when in fact there are
18 so many other components for pain management. So
19 again, thank you for allowing me to take part in
20 this.

21 DR. STAFFA: Thank you very much for
22 providing your input.

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1 Does anybody want to add anything else?
2 Again, what I heard was the MME being part of the
3 opioid dose, that's one characteristic, and that's
4 what that's looking at. But I heard a lot from
5 both the scientists, as well as the patients, about
6 how there's so much more.

7 Any comments on some of these other gaps of
8 what we need to know? I remember Dr. McPherson
9 even mentioned this idea that a calculator is
10 certainly not going to give you the full answer.
11 So I was wondering if folks wanted to just discuss
12 a bit about some of the other patient-level factors
13 around both using this as a conversion or rotation
14 tool, as well as the risk-prediction tool.

15 Dr. Fine, did you want to jump in here?
16 DR. FINE: Yes. Penney, thanks for always
17 bringing us back to reality and putting our feet
18 squarely on the earth.

19 Dr. Mellon, I think in his slide
20 number -- if I got it right down here -- 47,
21 summary slide 10, I think you pointed out
22 18 variables that might confound or at least create

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1 complexity amongst this notion of this construct we
2 call MME.

3 That's just 18 variables around MME. Now
4 you take the larger universe, or the world of
5 people living with debilitating pain, as Penney
6 pointed out, where there's a whole host of a myriad
7 of other variables -- and I won't list them here;
8 Penney's done a very good job of doing that -- so
9 you have a universe inside of a universe.

10 There's no way that sorting out the MME
11 issues can sort out more globally the issues we're
12 facing with adequate approaches towards treatment
13 of debilitating and persistent pain. We've got to
14 start somewhere, and this is a piece of it.

15 I know I'm jumping to a large conclusion
16 maybe at the end, but it would certainly seem that
17 in parallel with this process, the FDA would be of
18 extraordinary service, maybe in concert with
19 CDC -- rather than as separate entities, but
20 working and collaborating -- and with stakeholders
21 and experts who are actually dealing with real
22 patients and real pain every day, in real clinical

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1 settings, to have a broader perspective of how this
2 fits into that.
3 We can't solve all of the problems at once;
4 we have to deal with them. But we can't pretend
5 that they're not very and powerfully
6 interconnected. So I would hope that one of the
7 takeaways from this workshop would be rapid
8 movement towards an ongoing separate but connected
9 approach towards a fresh look at the construct of
10 debilitating pain, independent from and sometimes
11 connected -- occasionally connected - to issues
12 around substance-abuse and misuse issues, but not
13 conflating the two, which has been done to
14 extraordinarily -- and I will underscore a thousand
15 times, extraordinarily -- perverse ends over the
16 last number of years. Thank you.
17 DR. STAFFA: Thank you, Dr. Fine.
18 I believe I see Dr. Sandbrink. Your hand is
19 raised. If you want to unmute yourself, and state
20 your name, and provide your comment?
21 DR. SANDBRINK: Yes. Friedhelm Sandbrink,
22 Washington, D.C., Veterans Health Administration.

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1 Thank you very much. I really certainly learned a
2 lot over the last couple days from these excellent
3 presentations.
4 One thing that comes to mind is that we have
5 to probably separate the tool, which maybe is MME
6 conversion that can be used in clinical practice,
7 from the implementation of this tool as some kind
8 of policy guidance or state regulations.
9 I feel like from the experience of our
10 healthcare system, when I talk about the risks of
11 opioid prescribing and guidance that we have done
12 in regard to opioid reductions, that we have been
13 very careful of making sure that the patient
14 factors, and the patient interests, and the patient
15 concerns are being included in the discussion and
16 moving away from the actual number of the dosage or
17 whatever the MME calculation is.
18 On the other hand, as we make adjustments,
19 we need to provide guidance to clinicians of where
20 they are with the medications that they utilize. I
21 think there are conversions that happen every day
22 in clinical practice that are needed, so the

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1 guidance must be there. But what we really
2 actually learned is we need to probably get much
3 better guidance not just about the analgesia, which
4 is often, from what I understand, the MME is being
5 used for, but when we make a conversion in regard
6 to opioid reduction, it is often more an MME level
7 in regard to preventing withdrawal. So maybe
8 that's the second set. Right?
9 Then we have an MME level in regard to
10 respiratory depression, and possibly an MME, as we
11 heard, that may differ also in regard to risk of
12 addiction. And it may be related to the different
13 subtypes and obviously whether it's a full or
14 partial agonist, and it ends up being very
15 complicated. For clinical practice, though, what
16 ends up is things are being simplified too much,
17 way too much, but at the same time we have to have
18 some guidance that can be of assistance in clinical
19 practice.
20 So I feel like maybe we need to emphasize
21 more the limitations of any kind of conversions
22 that we have, whether that's for analgesia, or

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1 whether that's for respiratory depression, or
2 whether that's for withdrawals, but also keeping in
3 mind, always keeping in mind, that this is just a
4 tool that should not be used in regard to certain
5 regulatory attempts or legislative attempts from a
6 broader perspective; the end of my comment.
7 DR. STAFFA: Thank you, Dr. Sandbrink.
8 Dr. Dasgupta, can you unmute yourself, and
9 state your name, and provide your comment?
10 DR. DASGUPTA: Yes. Good afternoon. This
11 is Nabarun Dasgupta. I think on a population
12 level, there are two things that come to mind,
13 listening to the last few comments here. One is
14 that the large data sets, whether it's claims or
15 PDMPs, don't contain really good patient-level
16 improvement metrics. Sometimes in EHR, we'll get
17 pain scores, but those are instantaneous measures
18 that aren't so sensitive to change. We don't get
19 much in the way of social determinants of health
20 and other things that are confounders, as well as
21 the outcomes that matter to patients. So until
22 those kinds of metrics are in the big databases, I

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1 think analysts are going to pick what's there and
2 what's convenient, which is ICD-10 coded outcomes
3 and things like that.
4 The second comment is with regards to
5 evaluation of state-level policy impacts. In North
6 Carolina, we've looked at the STOP Act, which is
7 our state's version of those with prescribing
8 limits and things like that. When we
9 interviewed -- I can't remember how many doctors
10 and other prescribers we interviewed, but it was
11 dozens, not over a hundred, and hospital
12 administrators -- what we heard repeatedly was that
13 the 90 MME number is really convenient as a
14 mnemonic for having a line after which you need to
15 pay little bit more attention.
16 That sounds kind of reasonable, but the
17 other type of comment that we had was that it's
18 something that the physicians can use to push back
19 on patients they're not comfortable with
20 prescribing higher doses. So it's kind of
21 externalizing the responsibility and saying, hey,
22 my hands are tied, this is the law, this is the

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1 recommendation. In those situations, it wasn't
2 usually like pain management practitioners, it was
3 more general practice and other specialties.
4 So I think we can give guidance, we can give
5 instructions, and have all sorts of guidelines and
6 whatever, but at a very human, physician-patient
7 level, there's something kind of psychologically
8 going on here, emotionally going on in that
9 encounter, which I don't know that additional
10 guidance is going to solve.
11 DR. STAFFA: Thank you, Dr. Dasgupta.
12 Dr. Zhang, can you unmute yourself, and
13 state your name, and provide your comment?
14 DR. ZHANG: Thank you. Can you hear me?
15 DR. STAFFA: Yes, we can.
16 DR. ZHANG: I think maybe Penney Cowan
17 raised her hand before me. I just want to make
18 sure I didn't jump the line.
19 DR. STAFFA: I believe we heard from
20 Ms. Cowan, and we can go back to her.
21 DR. ZHANG: Thank you.
22 DR. STAFFA: Ms. Cowan, is your hand raised

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1 again or did you not put it down from before?
2 MS. COWAN: No, I'm good. I'm done. Thank
3 you. Sorry.
4 DR. STAFFA: Thank you so much. No, that's
5 alright.
6 Go ahead, Dr. Zhang. Thank you for being so
7 courteous. Go ahead.
8 DR. ZHANG: Thank you. This is Kun Zhang
9 from CDC. Just one follow-up and response to a
10 question that, Judy, you asked about, gaps at
11 patient level.
12 First, the comment is I really enjoyed this
13 discussion in the afternoon; very helpful. I think
14 there are a lot of points, good points, made by the
15 panelists that reflect, unfortunately, there has
16 been a lot of miseducation on the CDC guideline,
17 including certain specific recommendations in the
18 guideline. That's just one quick comment to what
19 we discussed previously.
20 To your question, Judy, the patient level,
21 the 1B here, I think we focused a lot on opioid
22 rotation and conversion. I'm not sure if this is

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1 already including opioid initiation, which I think
2 is also an important topic to consider here.
3 For instance, I know yesterday, several
4 speakers, they all mentioned, including
5 Dr. McPherson - I remember one slide. The first
6 point was to assess whether opioids should be the
7 choice, opioid therapy. I think opioid initiation
8 should be an important topic here, although we know
9 from the data that in the past several years, what
10 we saw that had decreased gradually the most is new
11 opioid initiation, including, for instance, a
12 short-day supply of opioid prescriptions probably
13 from dentists or from ER.
14 But I just wanted to give an answer to the
15 question you asked. Thank you.
16 DR. STAFFA: Thank you very much for
17 bringing that up. So you're pointing out the need
18 to better understand when opioids should be
19 initiated, so that's not really an MME calculation.
20 You're suggesting that that's more a consideration?
21 DR. ZHANG: Including the dosage for
22 initiation.

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1 DR. STAFFA: I see. I see. Great. Thank
2 you for clarifying that point.
3 DR. ZHANG: Thank you.
4 DR. STAFFA: Are there any other comments at
5 this point? I know question 1 is very, very broad,
6 so I have a feeling we're going to be coming back
7 and revisiting it as we move along. But I wanted
8 to suggest that we move to question 2, again,
9 knowing that there's a lot of overlap between these
10 questions.
11 But I think folks have raised a lot of
12 issues around the drug considerations; the other
13 outcomes other than analgesia that are not
14 currently considered in MME calculations; the idea
15 of the patient factors; and again, as Dr. Dasgupta
16 had mentioned, this idea of needing to better
17 understand and develop the science around
18 evaluation because many times big data are used for
19 those kinds of evaluations.
20 So I'm going to move to question 2. This is
21 where we want to talk about if you have thoughts
22 and ideas of the different types of studies and

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1 designs. I think several folks have mentioned the
2 lack of prospective trials. So if folks have
3 comments or anything they want to share further on
4 that front, and also talking about perhaps some of
5 the nonclinical versus clinical types of studies
6 that you would want to see in this space to
7 support, again, the use of MMEs for a number of
8 different applications.
9 Any thoughts on that?
10 It looks like Dr. Bettinger. Would you like
11 to unmute and state your name first?
12 DR. BETTINGER: Sure, sure. It's Dr. Jeff
13 Bettinger again. I just wanted to kind of throw
14 some ideas out. This is another topic that I'm
15 sure could go on and on, but more around what
16 Penney was saying before about thinking about our
17 patients, especially the chronic, intractable pain.
18 When we've looked at a lot of MME studies,
19 the initial studies, a lot of them, when they
20 center around and focus on analgesic effects and
21 looking at equal analgesic effects, a lot of it is
22 acute pain, it's post-operative, it's short term.

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1 It's not often we're seeing these studies in
2 chronic-pain patients.
3 So again, from that context, if we want to
4 look at what are some relative equal analgesic
5 effects of some of these opioids for the purposes
6 of, again, maybe an opioid rotation if someone's
7 not responding to an opioid anymore at a patient
8 level, can we look, or is it possible to study
9 patients with chronic pain, and maybe patients with
10 chronic pain conditions that are not as common.
11 A lot of times when we look at chronic pain
12 studies, it's in those with lower back pain, which
13 makes sense. That's certainly one of the most
14 common pain etiologies, but what about those with
15 fibromyalgia? What about those with Ehlers-Danlos
16 syndrome? What about those with trigeminal
17 neuralgia?
18 Even though it's certainly more rare in the
19 respect that, yes, you want to get in the funding
20 and things like that, but I think part of how we
21 start to establish some of those gaps are in
22 patient populations that are often the most

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1 vulnerable to pain and sometimes are the ones that
2 are highest opioid users just because of the pain
3 itself and the etiology itself, yet we don't have
4 many studies in these patient populations.
5 So I think as Penney alluded to, looking at
6 those different patient populations that are really
7 being affected by a lot of these policy changes
8 that are occurring at a lot of different state and
9 payer levels could be a huge way of at least
10 starting to look at some of these gaps. Thank you.
11 DR. STAFFA: Thank you for that comment.
12 I'm wondering, that you mentioned looking at
13 these patients; it seems like you could also be
14 looking at some of these other outcomes. Right?
15 Because if we're going to be applying MME limits or
16 some kind of policy to these patients, it that
17 would be helpful to understand whether that also
18 predicts some of the other concerns we have --
19 DR. BETTINGER: Yes.
20 DR. STAFFA: -- such as depression and,
21 again, whether different routes affect it. It
22 seems like you might also be able to examine some

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1 of these other factors and other issues that are
2 not currently considered in the calculation.
3 Would that be a fair statement?
4 DR. BETTINGER: Absolutely. Yes. And I
5 thank you for bringing that up because it is
6 looking at those other functionalities like you
7 said, depression, anxiety, mood, as really Penney
8 alluded to in that introductory presentation, and
9 going back to John Bonica and understanding pain is
10 multifactorial. It affects several different types
11 of things at a lot of different levels for
12 individual patients and their families.
13 So trying to incorporate more broad outcomes
14 and looking at other things just besides what's the
15 decrease in pain score itself. Absolutely.
16 DR. STAFFA: Thank you. Thank you,
17 Dr. Bettinger.
18 I'm going to be mean here, and I'm going to
19 pick on Dr. Comer.
20 Dr. Comer, I'm wondering, since a lot of
21 your work has looked at some of these other
22 outcomes and these other effects, I'm wondering if

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1 you have any thoughts on some of the clinical
2 studies that might be the natural next steps for
3 some of the work -- that you and your colleagues at
4 the University of Kentucky, Dr. Babalonis as
5 well -- that you guys have conducted.
6 Do you see clinical studies that might serve
7 as a good next-step here to your work?
8 DR. COMER: Yes. I've been sitting here
9 thinking about some of the challenges that we face
10 in our work.
11 DR. STAFFA: And I'm sorry to interrupt.
12 This is, Dr. Comer, right? I just want to say for
13 the record, this is Dr. Comer.
14 DR. COMER: Yes. This is Sandy.
15 Shanna and I are both used to doing studies
16 where we try to control things very carefully, do
17 time-effect curves, dose-effect curves, double-
18 blind conditions of dosing parameters and things
19 like that. There are all kinds of ins and outs of
20 doing that kind of research, and we've figured out
21 how to do it.
22 It's relatively simple to do it in a normal

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1 healthy volunteer population, even recreational
2 drug users. As Shanna mentioned in her
3 presentation, it's another level of complexity to
4 study people who are physically dependent with
5 opioid-use disorder, but we've kind of worked out
6 the parameters of how to do that.
7 Working with pain patients is kind of a
8 whole other ball game in the sense, as people have
9 described throughout these two days, that there are
10 so many layers of complexity with that patient
11 population, and trying to get a handle on, at least
12 from my perspective, the abuse liability of opioids
13 in that population is even doubly, triply
14 complicated for a whole bunch of both ethical and
15 scientific reasons.
16 The ethical reasons are that you have
17 somebody who's telling you that they're in chronic
18 pain, so from an ethics perspective, you don't want
19 to put them on nothing. So you have to have them
20 on a medication that we feel would be successful in
21 controlling their pain, so we've done that with
22 buprenorphine, for example. But then when you do

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1 that, trying to understand the abuse liability of
2 an opioid on top of that gets really complicated.
3 We tried to do that. We recruited people
4 who had chronic pain and were misusing their
5 opioids, and we put them on sublingual
6 buprenorphine 4 times a day. Then we thought,
7 okay, if we can push the dose high enough, we can
8 look at the abuse liability of oxycodone under
9 those conditions, for example, with the thinking
10 that maybe clinically it would be analogous to
11 somebody using oxycodone as a breakthrough
12 medication.
13 But what we found was that all of the doses
14 of buprenorphine that we were testing completely
15 blocked the effects of oxycodone, and we were
16 actually also comparing it to morphine. We went up
17 to an acute dose of 360 milligrams of morphine and
18 got no effect of morphine at all.
19 It was just like, okay, that's a
20 ridiculously high dose, and we gave up to
21 180 milligrams acutely of oxycodone. Same thing;
22 there were no ratings of drug liking, no ratings of

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1 feeling high, nothing, and they were only
2 maintained on 4 milligrams of sublingual
3 buprenorphine. So it's like we were scratching our
4 heads, how do we do this? How do we do this kind
5 of research?
6 Then on top of that, the scientific
7 complications are that these patients who have
8 chronic pain, who are misusing their opioids -- as
9 I kind of touched on this earlier today -- they may
10 be taking the opioids for two reasons. One is that
11 they want to get high, so that's the positive
12 reinforcing effects of these drugs, but then
13 also -- and someone else touched on this as
14 well -- they're using it to remove the pain.
15 So we had to come up with a whole list of
16 questions that we asked that said, "I like the drug
17 because it removes my pain. I like the drug
18 because I felt that euphoric effect." So it adds a
19 whole other level of assessment that we haven't had
20 to do before. It's tough. I know it's a long-
21 winded answer to your question, but --
22 DR. STAFFA: Oh, no. It's helpful to hear

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1 some of the challenges and complexities from people
2 who do this work. So yes, it's not
3 straightforward. Thank you for sharing that.
4 Dr. Babalonis, did you have anything to add
5 to that?
6 (No audible response.)
7 DR. STAFFA: Okay. Well, please raise your
8 hand if any other thoughts come to mind.
9 Dr. Fine, did you want to weigh in on this
10 topic or did you have a different topic to discuss?
11 DR. FINE: Yes. I wanted to sort of keep
12 the discussion going. I guess I'm finding myself
13 in that respondent situation where I'm stimulated
14 by all these comments, and it makes me think of
15 other things.
16 First of all, on the host presenter chat,
17 there are many other papers we could cite, but I
18 threw in three of them that date back 10-12 years
19 ago. And the reason I did was because there's
20 certainly some new science, and we need to
21 understand how to integrate that. But a lot of the
22 questions we're asking, the focus is really more

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1 sociology. The pharmacology is complex enough, but
2 what's really complicated is people and the whole
3 person.
4 We don't need to fully reinvent the wheel.
5 With some of these questions, the question you've
6 got is question number 2 and has been addressed in
7 the past in various forums, including at the FDA in
8 2013 at that meeting. I don't know if anybody else
9 was -- I can't remember who was there, other than
10 myself.
11 That sort of didn't go anywhere, and I don't
12 know what happened with those proceedings. But
13 there certainly has been a lot written about what
14 do we need to know and how would we proceed to
15 knowing it. So I at least wanted to provide a lot
16 of those thoughts that have been in published form
17 to reinvent the wheel.
18 Dr. Comer really underscores this question
19 why. We really have not put in the time or effort
20 to understand these various cohorts of individuals,
21 who we call patients, who behave in a whole host of
22 different ways and they're motivated by a whole

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1 host of different things. Sometimes they're
2 overlapping; that is they're motivated by pain.
3 Some people end up being motivated by drug use that
4 turns into misuse and abuse that has nothing to do
5 with pain, but sometimes it's overlapping. They
6 may be very different or overlapping cohorts of
7 patients, and we have not adequately understood
8 that.
9 In my own personal experience and practice
10 for almost 40 years, we maintain an
11 interdisciplinary pain management approach here,
12 which has been, nigh, almost impossible to do, but
13 we struggled to do it. We take all those
14 individual aspects of people -- sort of the
15 biopsychosocial/spiritual model -- very seriously
16 and try to integrate all that.
17 But what remains is there is a population of
18 individuals, without using opioids as a tool, that
19 would not have near any kind of quality of life or
20 functionality. And some of these patients are on
21 relatively modest doses of opioids, and some are on
22 what we would call maybe intermediate, and others,

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1 what might be called high doses of opioids, and
2 they may be absolutely indistinguishable from each
3 other in their overall behavior outcomes.
4 Some of these patients we've been following
5 for 25 or up to 30 years, and they don't dose
6 escalate. They are adherent to the plan of care.
7 They appear, in terms of how they behave and
8 function in their lives, like most of the people on
9 this conference call. They don't have a use
10 disorder. They are not debilitated by
11 psychological/psychiatric issues once their pain is
12 managed effectively, and opioids become a
13 critically important part of that, and they seem to
14 manage well.
15 We don't understand the differences amongst
16 these individuals and others who have problematic
17 use behaviors, or have adherence problems, or would
18 start out with a use disorder, and then we still
19 have to manage and maintain pain relief one way.
20 The methodology has really not been well
21 established of how to sort out those cohorts, how
22 to separate out and understand those variables,

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1 both at the pharmacological level and the
2 sociological level. Although there are ideas, I
3 don't think we're going to come to any great
4 conclusions here today; it's a deep issue.
5 But one thing that's absolutely for sure,
6 there has been no investment in doing this, and
7 it's unlikely that -- the pharmaceutical companies
8 are not motivated to do this. They're not rewarded
9 for that. The kind of information that comes into
10 FDA, I know in reviewing those data, doesn't ever
11 really get to that in terms of phase 1, 2, and 3
12 trials for drug approval.
13 Until NIH takes this seriously and makes an
14 investment in a methodology, and is willing to
15 commit to doing the kind of methodologically sound
16 trials that would allow us to understand and ferret
17 out the differences and what makes people behave
18 differently under different circumstances, I think
19 we're going to be spinning in circles.
20 I'm not nihilistic about this. I just think
21 that even a registry model, which has come up as an
22 alternative, sifting through and sorting that out,

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1 I'm not sure we've got the computing power or the
2 insight to enter in those variables, certainly for
3 any typical clinical record as of yet, without
4 capturing a cohort of individuals.
5 For instance, on high-dose opioid therapy,
6 who appear to be functioning very well, making them
7 a discernible study group and trying to understand
8 why they are the way they are, as an example.
9 DR. STAFFA: Thank you, Dr. Fine.
10 DR. FINE: Thanks.
11 DR. STAFFA: Dr. Comer, did you want to make
12 another comment?
13 DR. COMER: I was just going to say that a
14 number of years ago, the IMMPACT group, the one led
15 by Dennis Turk and Bob Dworkin, they organized I
16 think it was a two-day meeting, bringing together
17 people with expertise in pain and people with
18 expertise in abuse liability, and it was a really
19 interesting interaction because we were trying to
20 get a handle on how do you assess the abuse
21 liability of opioids in patients with pain.
22 One of the things that I took away from it

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1 is like, wow, we're really speaking different
2 languages. I guess I would just want to recommend
3 that that would be something I think that would be
4 helpful to the field, is if the two areas talk
5 more.
6 I know we've tried to do that, and that's
7 what Bob and Dennis were trying to accomplish. If
8 we can do that successfully, I think that that
9 would help move us forward in terms of the science.
10 DR. STAFFA: Right, right. Sometimes it
11 takes more than one try to get two groups of
12 people, one speaking Greek and one speaking Latin,
13 to actually move ahead. I agree.
14 Since Dr. Fine had brought up NIH, I have to
15 take that opportunity to see if our colleagues from
16 NIDA have anything they wanted to jump in and add,
17 or speak to, or think about as we consider this
18 idea of these kinds of clinical studies, perhaps
19 looking at abuse liability and patients with
20 chronic pain.
21 Any thoughts on that from Dr. McCann or
22 Dr. White?

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1 DR. McCANN: Yes. Hi. This is Dave McCann.
2 I have to say I work on the medication development
3 side of things and working to develop new drug
4 addiction treatment products, and overdose
5 treatments, and so forth. I have learned an awful
6 lot during this past day and a half.
7 It's just slightly off topic, but one thing
8 that I have to mention is that, really, in the long
9 run, not having to deal with these issues and
10 having safer more effective analgesics that are
11 less addictive, that has to be one of our long-term
12 goals, and we are doing a lot in that direction.
13 Unfortunately, it takes quite a while for
14 those new products to come to market, but a lot has
15 begun with the increased funds that were set aside
16 for the NIH HEAL Initiative, not just for addiction
17 treatment, but working to develop new analgesics
18 that won't have this type of baggage; that won't
19 put us in this kind of situation.
20 That doesn't really directly address the
21 question of talking about clinical trial design and
22 dealing with these MMEs, but I think it's got to

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1 give some people hope up there that we won't be in
2 this situation ten years from now.
3 DR. STAFFA: Thank you, and thank you for
4 making us aware and reminding us of that important
5 work that's going on under the HEAL Initiative.
6 Dr. Comer, did you have another comment to
7 make on this topic?
8 DR. COMER: Yes, just a response to Dave's
9 comment. This is Sandy Comer.
10 Thanks for reminding us about the HEAL
11 effort in this direction. I also attended the HEAL
12 investigators meeting very recently. I was excited
13 about this one medication that we're working with,
14 from the perspective of treatment medication for
15 opioid-use disorder. It has this really
16 interesting pharmacology that has an opioid
17 component and serotonin and norepinephrine
18 components as well. It produces analgesic effects
19 in preclinical models, but tolerance doesn't seem
20 to develop to it or physical dependence.
21 It's kind of a unique molecule, but it could
22 be potentially used for treating pain as well. But

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1 it was clear from the discussion at the meeting
2 that they're not interested in funding anything
3 that has any kind of opioid component. Even in
4 both rodents and primates, this substance doesn't
5 have abuse liability. So it's just like, well,
6 we're kind of stuck.
7 DR. McCANN: Well, given that NIH is a very
8 large group, because one group isn't interested, it
9 doesn't mean you won't be supported by another
10 part. I think a lot of the analgesic work that is
11 opioid related tends to come to NIDA, and many of
12 the projects that are not, end up going to NINDS.
13 So there are other institutes. One group
14 may be more interested in one project than another,
15 but I certainly wouldn't give up on a product like
16 that moving forward for analgesia just because you
17 got some negative comments. When an application
18 comes into NIH, they'll decide which institute it
19 goes to, and I would keep that in mind. There's
20 still another direction it might be able to go.
21 But it is very exciting, the number of
22 different approaches that are being taken. There's

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1 one that actually predates HEAL. Many years ago,
2 we worked with the folks in the Dental Institute to
3 move a compound along. It's called
4 resiniferatoxin. I can't figure out how to type
5 into the main box here or I'd spell that for you
6 all. It's also sometimes abbreviated RTX.
7 We worked to help get that into the initial
8 clinical testing, and then there's a private sector
9 pharma company working on moving it forward.
10 They're actually looking at injecting it into the
11 knees in folks with severe arthritis, so it seems
12 to be helping quite a bit. This is something that's
13 not going to affect respiration at all.
14 So it's just one example. There are many
15 approaches that I think, again, ten years from now,
16 hopefully we'll have a lot less need to use opioids
17 that are so dangerous.
18 DR. STAFFA: Thank you.
19 And just for the record, that was Dr. McCann
20 speaking. I just want to make sure they
21 appropriately attribute those remarks, Dr. McCann.
22 DR. McCANN: Oh, that's right.

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1 DR. STAFFA: No problem.
2 I had a question from my FDA colleagues for
3 Dr. Comer. The study you had described, where
4 patients had been on buprenorphine, and then you
5 had added morphine, they were wondering, do you
6 think it would be possible to do a study like that
7 but using a different agent than buprenorphine?
8 Might that produce a more meaningful finding?
9 DR. COMER: Yes, it could potentially. We
10 chose buprenorphine because it's a bridge between
11 treating pain and treating opioid-use disorder.
12 But yes, we could look at another opioid. I think
13 it's just a matter of tweaking the model so that we
14 can get the information that we want. But yes,
15 that's definitely a possibility.
16 DR. STAFFA: Okay. I just wanted to make
17 sure that was addressed.
18 Dr. Dasgupta, did you want to chime in? If
19 you can unmute yourself and state your name.
20 DR. DASGUPTA: Sure. This is Nabarun
21 Dasgupta. Thanks, Dr. Staffa.
22 I think the population scientists should

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1 also be in the room with y'all talking about
2 clinical pharmacology and the clinical trials. I
3 think right now there are a lot of folks who are
4 never going to be represented in a clinical trial,
5 and some of those folks are using non-
6 pharmaceutical opioids.
7 So right now a lot of the conversation that
8 we're having here with the pharmaceutical realm is
9 also happening on the street with unregulated,
10 illicitly manufactured opioids.
11 In North Carolina, we are testing discarded
12 baggies and other drug samples to really understand
13 what's in heroin and the different isomers,
14 enantiomers, and all the other molecular opioids
15 that we're seeing, and some of those are very
16 different. When those particular batches hit the
17 streets, the folks who are working frontline
18 programs can tell, pretty much within a couple days
19 to a week, which kinds of people are going to be
20 interested in which types of those atypical
21 opioids.
22 A lot of that happens without any

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1 pharmacology insight, but you do see particular
2 batches of, quote-unquote, "heroin," where people
3 who are really into the ketamine type stuff or
4 really strong body dissociatives will really go
5 after a particular batch of heroin, and 90 percent
6 of folks will absolutely not touch it and even
7 throw it away.
8 So there's a lot of additional insight
9 that's happening right now because of the
10 unregulated opioid supply, which might be explained
11 by some of this pharmacology and might inform some
12 of the clinical liking patterns that you guys seem
13 to be interested in studying from a sociology point
14 of view as well.
15 DR. STAFFA: Thank you for bringing that up.
16 That's a great point. And I would add to that,
17 that I think having the epidemiologists and
18 population scientists in the room with the pain
19 management and folks who study abuse liability
20 would be helpful, because given some of the ethical
21 issues that people have talked about and the
22 complexity of these studies, there may well be some

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1 role for nonrandomized or observational designs,
2 so-called real-world data, to perhaps supplement
3 and complement some of that work.
4 So thank you for bringing that up. We'll
5 definitely get you an invite if we can get that
6 meeting on the calendar.
7 Dr. Fine, did you want to add in another
8 comment here?
9 DR. FINE: Yes, again to be responsive, and
10 maybe a little more of a social note, one of the
11 things we lose in having this virtual meeting is
12 the collegiality that we've all, I think, enjoyed
13 in years past, where we can reconnect.
14 Nab Dasgupta, it's great to hear your voice
15 again. It's been way too long since we've hung out
16 and tried to heal the world together. I can't see
17 you and we can't communicate across the table, but
18 I just wanted to note there are a lot of
19 individuals on this call. It's really wonderful to
20 reconnect. I wish we could be around in person,
21 but obviously we can't.
22 That said, Dave McCann, Nab, and Sandy

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1 Comer, these are very important points. But I
2 think there's also a reason -- I'm not a
3 psychologist, I don't even play one on TV, but I've
4 hung around them long enough now to maybe be a
5 little bit aware of what motivates people; if not
6 myself. As Dave McCann said, the NIH is a very big
7 organization, and there have been attempts at
8 bringing groups together.
9 But maybe as more of a political comment
10 than anything, there was tremendous resistance and
11 has never been an adequate response to the huge
12 public health problem, if you will, if you want to
13 call it a problem, of millions of people, tens of
14 millions of people, at extraordinary costs. In
15 fact, the last effort to look at this attributed
16 something on the order of between \$800 billion and
17 a trillion dollars of costs related to intractable
18 or debilitating pain in this country, which I think
19 added up was greater than heart disease, diabetes,
20 and cancer combined.
21 Yet, there still is no institute of pain or
22 either clinical research within NIH. There is the

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1 IPRCC, the Interagency Pain Research Coordination
2 Advisory Committee, but it's an advisory committee.
3 And there are some brilliant people and very
4 dedicated people on that, but until there's a
5 championing, motivating, this is your daily work,
6 this is your career, this is what your ego
7 requires, et cetera, I think we're not going to get
8 to that place that we all sort of say we want to
9 get -- no less able -- and connect the bridges
10 between NIDA and this prophetic institute of pain.
11 So I think there's very good reason we have
12 not progressed much in the last ten years over
13 this, and we have more questions than answers.
14 Maybe that's something that could come out of FDA,
15 as a branch of Health and Human Services, is an
16 acknowledgment that until such time as we truly
17 commit whole hog, and put our egos, and our
18 professionalism, and our careers, and have
19 committed resources behind it, maybe we're going to
20 continue to spin wheels.
21 Again, I'm not a nihilist; I'm highly
22 optimistic. But there's a reason that IMMPACT

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1 never went forward, and HEAL is all about
2 non-opioid, and so forth.
3 I just had to smile, Dave, at your comment
4 about maybe ten years from now. I remember in my
5 typical impassioned way, as you can sort of hear
6 it, standing up at several meetings, including FDA
7 meetings, and the Office of the White House's
8 National Drug Policy, and so forth, more than
9 ten years ago, saying, "Ten years from now, we
10 won't have to have these discussions because I know
11 we'll have drugs that will not have abuse
12 liability, but for the meantime, we need to get
13 good at what we have."
14 Well, 10, 12, 15 years has passed, and we're
15 still there. I'm afraid if we don't do something
16 more focused and intentional, we'll still be here
17 in 2030, having the same discussions. That's my
18 grievance.
19 DR. McCANN: This is Dave McCann jumping in.
20 I agree. I think ten years seems like a long time
21 when it's in the future, but then it goes by really
22 quick, and you're right back where you were.

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1 I just have to say that, personally, I agree
2 it would be fantastic if we had a pain institute.
3 I see even communication challenges within an
4 institute, between divisions and so forth. While
5 we do have a trans-NIH pain initiative group,
6 representatives from different institutes getting
7 together to focus on pain, I think it would be
8 fantastic if we had a pain institute.
9 I understand that there is a limit to the
10 number of institutes and centers that NIH is
11 allowed to have, and I think that may be what's
12 holding it back. You just look at the list and say
13 which one do you cross off to create a new one.
14 Maybe that needs to change.
15 DR. STAFFA: Great. Thanks for taking that
16 one, Dr. McCann.
17 Okay. I'm going to move us over to
18 question 3. And again, if there are other thoughts
19 of creative or innovative types of studies, or
20 designs, or issues you'd like to raise or you want
21 to bring up in later questions, we can certainly
22 revisit that.

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1 Question 3, I guess I want to kind of probe
2 a little bit on some of the factors we didn't talk
3 about a lot in our previous discussions. We kind
4 of touched on, I think, a lot of the drug
5 considerations, the issues around drugs, like
6 buprenorphine, and tapentadol, and methadone, and
7 some of the outcomes beyond analgesia as an
8 outcome, and some of the other outcomes that are
9 worth comparing and understanding different opioids
10 and their relationship to each other on.
11 But I wanted to just get folks' thoughts
12 about what are some of the other key factors that
13 we heard about a lot yesterday and again today
14 about patient and population levels, issues that we
15 need to make sure are brought into some of these
16 studies, whether they're preclinical studies,
17 whether they're nonclinical studies, or whether
18 there are some of the studies we talked about in
19 patients with chronic pain and those kinds of
20 populations, too.
21 I think folks have brought up the point that
22 these are populations that have not really been

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1 adequately studied in terms of understanding some
2 of the outcomes here, and really understanding what
3 happens to patients over time and what some of the
4 risks may or may not be.
5 Any other thoughts folks would like to add
6 in terms of priorities for our research agenda in
7 those areas, things we haven't yet touched on that
8 might have been brought up in the talks you've
9 heard, or not brought up, but occurred to you based
10 on the work that you've done?
11 Dr. McPherson, would you like to unmute
12 yourself and state your name and make your comment?
13 DR. McPHERSON: Lynn McPherson, University
14 of Maryland. It just occurs to me that perhaps we
15 should be considering doing some qualitative
16 research along with this and looking at the
17 perceptions of prescribers.
18 I think what's really made things kind of
19 hit the fan is prescribers are scared to death to
20 write for opioids and they're so fearful of these
21 limits, even though the CDC is very clear this is
22 guidance. It's not carved into a tablet brought

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1 down from the mountain, but people are very fearful
2 and patients are paying the price. So perhaps
3 doing some qualitative research in this area would
4 be beneficial. That's it.
5 DR. STAFFA: Thank you very much. That's
6 very helpful.
7 Do folks have other thoughts they want to
8 contribute? That's a little different from what
9 we've heard, so yes, that's something we can
10 definitely bring in, and more in the social science
11 area.
12 Dr. Chidgey, would you like to state your
13 name and provide your comment?
14 DR. CHIDGEY: Yes. This is Brooke Chidgey
15 from UNC. I think that makes a lot of sense. I
16 know as a pain provider myself and prescriber, what
17 we see is a lot of the physicians and prescribers
18 in the community just refusing to prescribe opioids
19 altogether. And while the CDC guidelines, as you
20 mentioned, are just a guideline, it's really been
21 taken much further than that, and further than
22 intended, and MMEs being used by medical boards,

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1 for example, and providers are scared.
2 I certainly have been afraid. When I do
3 what I think is right, I do wonder sometimes am I
4 going to get in trouble for what I'm doing, even
5 though I think it's very medically appropriate and
6 sound, but because of the ramifications that go
7 along with prescribing a high-dose opioid and it
8 being flagged. Thank you.
9 DR. STAFFA: Thank you. Yes, those are very
10 good points.
11 Dr. Comer, would you like to make a comment
12 here?
13 DR. COMER: Yes, just a suggestion for
14 research questions. It would be really
15 interesting, I think, to measure MMEs as they
16 relate to other endpoints like quality of life, and
17 drug craving, and some of these endpoints that I
18 don't think we pay enough attention to, because I
19 would imagine that quality of life will go down as
20 the MME goes down.
21 So just a thought; I don't know. These
22 patients seem like they're not functioning very

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1 well at all with these lower doses that are being
2 prescribed nowadays.
3 DR. STAFFA: Right. No, that's actually a
4 very good thought.
5 For the transcriptionist, that was
6 Dr. Comer.
7 I also wonder, as we think about it, that
8 I'm intrigued by the idea of trying to understand
9 better what prescribers are thinking, and the
10 pressures they're under, and articulating that.
11 I'm wondering if folks could think about whether
12 there might be any value -- I know that there were
13 some conversations yesterday about getting
14 pharmacists more broadly involved in these issues,
15 of having that expertise more broadly brought into
16 pain management in a more global way to provide
17 some of the insights into patient care that we
18 heard Dr. Fudin, Dr. McPherson, and others discuss
19 of how important that role is. I wonder if there
20 might be studies that could be done to demonstrate
21 the value of that in different environments.
22 Let's see. Let me go back. I believe,

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1 Dr. Fine, you were next.
2 DR. FINE: Yes. I wanted to pick up on that
3 theme of -- and every time Sandy Comer talks, I
4 always think about what's this interface between
5 people living with pain, but also what are some of
6 the other affective or motivational issues around
7 their behaviors around medication use.
8 I'll just give an example, and I'd love to
9 hear people's comments about this. It's a very
10 typical patient. It's sort of tied to a
11 prototypical patient, so I don't give any
12 confidential or patient-specific information.
13 Let's say a woman with a very severe or
14 debilitating chronic pain has both neuropathic and
15 musculoskeletal components to it. There are no
16 interventional therapies that have proved helpful,
17 underwent a lot of cognitive behavioral therapy,
18 and is very good at maintaining and managing her
19 diet, exercise, behavioral issues, and insight into
20 mindfulness, and all the kinds of things that are
21 helpful and all, but was able to, and has been able
22 to, essentially lead a normal life, including a

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1 professional normal life, up to the point of
2 retirement a few years ago, say, using a
3 100 milligrams of extended-release morphine every
4 8 hours around the clock and 30 milligrams of
5 morphine, up to 3 doses a day, for so-called
6 breakthrough pain, and has been fully adherent and
7 adheres strongly to urine drug testing, controlled
8 substance database checks, and that kind of stuff.
9 The question I've been asking myself for the
10 last 20 years, being involved in her care, is how
11 much of the additional opioid, other than the
12 around-the-clock opioid, is used to manage
13 something other than an end-of-dose failure, or
14 resurgence of pain, or some perceived reduction in
15 blood levels that leads to -- she says what's
16 motivating is that when she takes this, it's
17 because she has more pain. But is that because
18 there's a little more stress, a little more
19 anxiety, a little more sleeplessness, something
20 else that enters into everybody's lives, or is it a
21 subliminal perception of a slowly but insidious
22 abstinence and craving? Is it a reduction in

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1 positive mood that's been drug-induced over time?
2 There's no evidence of hyperalgesia going on that's
3 discernible.
4 But how do we -- and this goes back to that
5 question that came up after -- gosh, I can't
6 remember -- the talk that ended with the slide that
7 had the green and red lines on it, trying to
8 discern the difference between substance misuse,
9 abuse, and motivations for that versus control of
10 pain, versus the management of other affective, or
11 emotional, or psychological phenomenology.
12 So that's a question wrapped up in a case
13 example, but I would love to hear you all's
14 thoughts about that. How would we even go about
15 studying something like that to make sense of this
16 without either bifurcating patients into they're
17 drug seeking, or they're pain seeking, or
18 pain-relief seeking? There seems to be a lot of
19 gray in between that we have not been able to -- or
20 haven't really discussed much.
21 DR. STAFFA: Thank you, Dr. Fine.
22 If others have comments on that, please do

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1 raise your hand, and we'll get to you.
2 Ms. Cowan, did you have a comment?
3 MS. COWAN: Yes. This is Penney Cowan, and
4 a couple of different comments for Dr. McPherson.
5 One of the things she talked about was the number
6 of people that were denied access, and we heard
7 that over and over again in the calls that we've
8 received from people who were fired by their
9 providers because they didn't follow the
10 agreements, which were put into place to prevent
11 overprescribing, and refilling too soon, and all
12 the other things that go with that.
13 But a lot of people had a difficult time
14 with access to care and trying to find providers.
15 Physicians would even put signs on their windows
16 that they are no longer prescribing. And again,
17 the sad thing is that it's never just about the
18 pain meds, but it seems to be that's what
19 everyone's expectation is, or many of them are.
20 Even offices were raided. A lot of pain docs, they
21 quit because they didn't want to deal with it
22 anymore.

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1 Talking about the pharmacists, we have done
2 a lot of work with the American Pharmacists
3 Association because we know that they are probably
4 one of the easiest people to get to, to really have
5 a conversation. We have a video on our webpage, in
6 chronic pain, called Taking Care, which talks about
7 all of the training that they have to help people
8 better manage their pain.
9 So they're not just there to dispense
10 medicine, but also to give that advice and to help
11 them. The only problem is they also have quotas
12 that they have to feed, so again, it goes back to
13 payment for time that they're spending.
14 Then one other comment about what Dr. Fine
15 just said, a lot of people with pain are very
16 isolated and alone. So while you may get them on a
17 maintenance dose, and they may be able to manage
18 their pain appropriately, even who are out there
19 working, people don't understand what it's like to
20 live with pain, and we don't typically talk about
21 it.
22 So maintaining your wellness is so very

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1 important, and one way to do that is through
2 peer-led support groups and talking with other
3 people. And I know that has nothing to do with
4 that, but I just had to put that in there, so thank
5 you very much.
6 DR. STAFFA: Thank you, and thanks for
7 reminding us of that because, again, these can be
8 elements of study design, looking at the complete,
9 all the different things that one needs to manage
10 pain.
11 Dr. McPherson, did you have another comment?
12 DR. McPHERSON: Yes. Lynn McPherson. Just
13 in response to what Ms. Cowan just said, I worked
14 in a primary care clinic for 29 years doing pain
15 management, and eventually at some point, the
16 physicians were just so uncomfortable with this,
17 they said, "That's it. We can't do any more pain
18 management." They all had to go to the specialty
19 clinic, which in no way could handle the volume of
20 patients. That was very sad.
21 But back to the comment about the
22 pharmacists, yes, we are completely adorable

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1 people. The pharmacist is the most commonly
2 accessed healthcare professional in the whole loop.
3 And under the law, pharmacists have a corresponding
4 responsibility to prescribers, relative to
5 prescribers, to also assure the safe and effective
6 use of opioids.
7 But I do fear that sometimes insurance
8 companies, with the drug benefit, as well as
9 large-chain pharmacies, have policy in place that
10 kind of puts the pharmacist in a role of the drug
11 police. So I just think we have some work to do
12 there. I continue to push for better education for
13 pharmacists in the community because they are
14 tremendous patient advocates, and they are the last
15 line of defense between individual patients and
16 society, and holding the line. Thank you.
17 DR. STAFFA: Thank you very much for your
18 comment on that.
19 And in full disclosure, I just want to make
20 sure I mentioned that I am not just an
21 epidemiologist; I am also a pharmacist. So I'm
22 just putting my biases out there for everybody to

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1 know.
2 Dr. Dasgupta, did you have a comment to make
3 about the issue about the role of the pharmacist?
4 DR. DASGUPTA: I think Dr. McPherson
5 actually just said pretty much what I was going to
6 say, although I don't know that I could say
7 "adorable" because I'm not a pharmacist myself.
8 But I think the administrative and
9 professional space that pharmacists have to operate
10 in is really constrained by their institutions.
11 And like the ultimate gatekeeper handing over a
12 prescription, I think that role, versus like a
13 caring role that takes more time, I think those are
14 kind of -- well, I wouldn't say at odds with each
15 other, but they're competing priorities.
16 We've done surveys of pharmacists' attitudes
17 about different opioid tools and different parts of
18 opioid prescribing, and we find that pharmacists'
19 attitudes are often more akin to emergency
20 department physicians, where they're
21 high-throughput seeing kind of people in the most
22 dire conditions, and those experiences really shape

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1 their views on how much compassion they can have
2 versus doing the biomedical thing.
3 Just my opinions, not as a pharmacist, but I
4 do agree with Dr. McPherson completely.
5 DR. STAFFA: Thank you, and thanks for
6 chiming in on that.
7 Dr. Chidgey, did you have something to add?
8 DR. CHIDGEY: Yes. Thank you.
9 Going back to the point by Dr. Fine about
10 the affective component of pain, I think there's a
11 really big thing that needs to be distinguished,
12 and that's distress and physical pain. And I think
13 in our country, mental health is very stigmatized,
14 so people often have trouble saying I'm depressed,
15 I'm anxious, but they don't have trouble saying I'm
16 in pain. And I think we see that a lot, where
17 people are using the opioids to try to treat those
18 other problems that they have.
19 We've done some studies on post-operative
20 patients who get opioids, and it was really
21 fascinating. We asked them how much they took
22 after their surgery and why they took it, and you

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1 got some people who took none, even though they had
2 pain because they were afraid. You had some people
3 who took all of it no matter how much they got
4 because they thought they were supposed to.
5 I think we see in a lot of patients in my
6 clinic that sometimes there's just a difficulty in
7 understanding what PRN truly means and as needed.
8 I feel like the majority of my patients who get
9 as-needed pain medication take it on a scheduled
10 basis, and I found there are a lot of different
11 reasons for that.
12 DR. STAFFA: Thank you for adding that in.
13 I think that's an important issue. It dovetails
14 with a question I'm getting from my colleagues,
15 which is in the area of quality of life. I think
16 the goal of treating any patient with chronic
17 pain -- and I think for many of the efforts of
18 utilizing MMEs -- is to have a better quality of
19 life.
20 What kinds of things? If folks could think
21 about, if we were able to actually support studies
22 looking at this population and wanted to make sure

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1 we did more than measure prescriptions for opioids
2 as an outcome, what would be the kind of measures
3 that might indicate different levels of quality of
4 life for such patients?
5 So if you can be thinking about that and
6 raise your hand if you have comments on that, that
7 would be wonderful.
8 Dr. Bettinger, did you have a comment next?
9 DR. BETTINGER: Yes. I just wanted to go
10 back to the original question and some of the
11 commentary, in addition to comment on the potential
12 role of pharmacists.
13 What we were talking about before, and even
14 what you had just brought up, Dr. Staffa, about
15 what else can we look at, I agree. I like the idea
16 of looking at more qualitative factors,
17 particularly around, as Dr. McPherson, Dr. Fine,
18 and others point out, physicians and MPTA
19 pharmacists.
20 What is the comfortability right now? I
21 think it probably speaks for itself that the
22 comfortability level around opioids has gone down

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1 drastically. If we look at studies on education,
2 not too, too much has changed in the realm of
3 overall education at any healthcare professional
4 level around opioids, around pain disorders.
5 So I think those are things that we could
6 continue to look at, and even take it to almost a
7 grassroots level with education resources. That
8 could be something headed by the FDA, the CDC, and
9 almost thinking of the realm of pharmaceutical
10 companies, the way they, especially in the past, go
11 into physician offices or hospitals and set up CE
12 programs directly to -- again, different types of
13 clinicians; I think if the government began to
14 maybe take some of those steps and, again, look at
15 where the education level is and where it could
16 improve in terms of comfortability.
17 I think that actually ties in, again, to
18 another role of the pharmacists. It's funny that
19 Dr. McPherson said she used to work in primary
20 care. That's actually what I do. I work across
21 seven different primary care clinics, about
22 30 different primary care providers, and I

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1 essentially help co-manage pain patients. I see
2 them. Oftentimes, I follow up with them on my own,
3 me by myself.
4 I certainly learned under Dr. Fudin, who was
5 of course on yesterday. You tend to be much more
6 comfortable around opioid use in terms of how do we
7 monitor, what questions to ask, even how to
8 approach those conversations with patients, whether
9 they're good conversations or difficult
10 conversations.
11 So I think that's a role of a pharmacist
12 that's more unique, but I think that can be
13 drastically needed, too. We do often think of a
14 pharmacist at the community setting, the CVS,
15 Walgreens, but there are a lot of pharmacists that
16 practice in clinical settings as well that have,
17 like myself, residency experience with different
18 types of practitioners, learning under
19 psychiatrists, and psychologists, and neurologists,
20 and substance-abuse counselors.
21 So I think there certainly is a component of
22 underutilization, still, and it comes back to

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1 billing and other things. But looking at those
2 types of underutilized resources and ways we can
3 improve care by utilizing those resources well, I
4 think could help when we're looking at these types
5 of clinical studies and outcomes. Thank you.
6 DR. STAFFA: Alright. Thank you for that
7 comment, and I agree with you. In fact, when I was
8 at the Rx Opioid and Heroin Summit earlier this
9 year -- well, I wasn't there actually, but when I
10 participated virtually, there were a number of
11 studies of looking and trying to understand the
12 needs of community pharmacists in this area.
13 It was looking more at naloxone provision
14 and dispensing, but it was clear that community
15 pharmacists may be in need of some education in
16 this space, and perhaps that may be an area where
17 we can explore studies to try to understand what
18 kinds of education and how it might be most
19 effective in this space.
20 Dr. Zhang, would you like to make a comment?
21 DR. ZHANG: Thank you. This is Kun Zhang
22 from CDC. I think we all share some great ideas,

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1 and I just want to piggyback on a couple of them,
2 for instance, conducting more quality studies and
3 assessing comfortability level of prescribers.
4 I just want to add, based on some
5 preliminary data we have, one interesting thing we
6 haven't touched is we observed a 20 percent
7 increase in nurse practitioner/prescriber of
8 opioids between 2016 and 2019. Of course, there
9 are decreases in other types of specialties for
10 prescribing opioids.
11 I think that's an interesting data point,
12 what was driving that and also who these
13 programs/practitioners work for, including nurse
14 practitioners and physician assistants. Of course,
15 from the data, we cannot tell whether they work for
16 primary care, or pain medicine, or surgeons.
17 Unfortunately, we don't have that information, but
18 I think that warrants additional investigation.
19 The second comment I want to go back to the
20 question on the slide. In addition to MME, at a
21 patient level, I think it's also important to do
22 more research around the specific indication for

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1 prescribing opioids, which is hard to tell from an
2 observational study or an ideological study. It's
3 very hard to figure that out from claims data.
4 I think it's important to differentiate what
5 the drug is prescribed for at an MME level,
6 probably by the indications of whether it's for
7 some surgical procedure, or a certain type of
8 chronic pain, or even a migraine. I don't think we
9 have good data points on that. That's another
10 area, I think, back to the question on the slide,
11 that warrants additional research and further
12 investigation. Thank you.
13 DR. STAFFA: Thank you very much for sharing
14 that.
15 I wanted to just chime in. Indication, I
16 think bringing that up, it is a real challenge,
17 especially when one's looking at big data, which is
18 often the way we can study and examine what's
19 happening in populations. I think perhaps if
20 there's a way -- I know in drug safety, for years
21 we've often supported work to try to do what we
22 call validation work to try to understand how often

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1 claims, or charges -- it's often billing
2 data -- are actually reflecting the actual
3 condition behind the billing claim in the patient
4 to make sure that we are looking at the drug safety
5 outcome that we think we're looking at.
6 I'm wondering if some of that work might
7 also be done to develop algorithms to better
8 understand how different indications appear in
9 claims data, because I think particularly in
10 patients who have chronic pain, those can be rather
11 complex, and not simply a single code but perhaps
12 more of an algorithm. So that is an area that
13 certainly could be --
14 DR. ZHANG: Yes, exactly. I agree.
15 DR. STAFFA: -- a science we could study.
16 DR. ZHANG: Thank you.
17 DR. STAFFA: Thank you, Dr. Zhang.
18 Dr. Parkinson, did you want to make a
19 comment?
20 DR. PARKINSON: Yes. This is Dr. Parkinson.
21 Just quick to go back to the comment about using
22 pharmacists, in the MHRA, and just generally in the

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1 UK, we're really encouraging the use of
2 pharmacists. For us, the education is the real
3 factor here, and we want to try and increase
4 education for pharmacists, as well as patients.
5 Patients need to know, too.
6 The pharmacists are basically there on the
7 front line, so they're able to actually give more
8 information to the patient, which they might
9 actually have forgotten when they've seen their
10 doctor.
11 Pharmacists are also able to see whether
12 that person has been in more than they should
13 really have been. They're able to shop. They're
14 able to see if a patient's a real person or if it's
15 actually someone who is just becoming dependent, or
16 overusing or something, and they're able to then go
17 back and say, "Well, you need to talk to your
18 doctor," or one thing or another.
19 Within the UK, we're definitely trying to
20 push the responsibility, or we're recognizing that
21 they have a level of knowledge that sometimes the
22 primary care physician probably might not have just

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1 because they see these patients, or they see the
2 area or the people that are coming through, and
3 they're familiar with a particular opioid or
4 medicine that they're having.
5 Physicians change and they move around.
6 Well, the same could be said for a pharmacist, but
7 they have a very specific educational base, which
8 is kind of different. So we are supporting that.
9 That's something in which we're trying to push and
10 trying to create more education around. Thank you.
11 DR. STAFFA: Thank you for sharing. It
12 helps to know that that's an issue that you guys
13 are also working on.
14 I don't know if you have the same challenges
15 in the UK, but here, pharmacists are often very
16 challenged by the pressures of prescription volume,
17 particularly those who work in large busy stores.
18 It can often be challenging to find time. And as
19 was brought up yesterday, pharmacists are often not
20 paid for their professional services in different
21 areas, and they've become particularly busy as
22 they've become vaccination sites during COVID of

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1 course.

2 So I think we would have to try to keep

3 those pragmatic concerns in mind as we think about

4 that and explore that as a topic for understanding

5 better what role they might be able to play.

6 Dr. Dasgupta, did you have another comment

7 on this topic?

8 DR. DASGUPTA: Just a quick one in response

9 to Dr. Zhang's observation of the increased number

10 of unique prescribers. I think that is directly

11 attributable to nurse practitioners being allowed

12 to prescribe. I think data that I've seen from

13 late 2019, I think early 2020, was that nurse

14 practitioners now prescribe more extended-release

15 opioids than MDs or other physicians do, in terms

16 of number of prescriptions.

17 So I think that's been a very big change,

18 but I think it's pretty consistent across the

19 country and linearly observable from the point at

20 which those DEA regs were liberalized.

21 DR. STAFFA: Great. Thanks for those

22 insights.

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1 I think, as the chair's prerogative, I'm

2 going to go ahead and suggest that we take our

3 10-minute break now before we move into questions 4

4 and 5, which are kind of related. These are going

5 to be tough. These are focused back on more of the

6 MME calculations, and the tables, and the

7 references.

8 So I want you to rest up, grab your cup of

9 coffee, and we'll see you back here at 3:25.

10 Thanks so much.

11 (Whereupon, at 3:16 p.m., a recess was

12 taken.)

13 DR. STAFFA: Welcome back, everybody. I

14 hope you got your coffee and stretched your legs.

15 Those were actually the easy questions we dealt

16 with already. Now we'll get to the really hard

17 ones.

18 Going back to a lot of what we heard, mostly

19 yesterday, are the real challenges of having so

20 many different conversion tables, and files, and

21 calculators. I wanted to just have folks discuss,

22 do we need a gold standard reference table, and

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1 what would we need to do to develop that?

2 If we were to be able to do something like

3 that, what do you think that the purpose for that

4 would be? What is feasible to use this kind of a

5 gold standard reference table? What kind of

6 benefit could we gain from it were we to go in that

7 direction?

8 We talked a lot about trying to understand a

9 lot of the concepts. The first three questions, we

10 talked a lot about trying to learn more about a lot

11 of the concepts that are not addressed by MME

12 alone. Is there a value that we could address with

13 such a reference table, and what might it be?

14 So if folks have thoughts about that?

15 (No response.)

16 DR. STAFFA: Don't all rush in at once.

17 Dr. McPherson, I knew I could count on you

18 to get the conversation going here. Go ahead,

19 please.

20 DR. McPHERSON: Absolutely. Lynn McPherson.

21 I think this question begs a bigger

22 question. Are you talking about calculating MMEs

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1 for limits by the insurance company or the state,

2 or are you talking about patient care? That's the

3 end of my question.

4 DR. STAFFA: I think here we're talking, at

5 this point for this question, the reference would

6 be used in patient care, because I think that's

7 where a lot of these online calculators are

8 currently. Let's start there, at least. Let's

9 focus on that need.

10 DR. McPHERSON: Can I continue my comment,

11 then?

12 DR. STAFFA: Please do.

13 DR. McPHERSON: Okay. Still Lynn McPherson

14 here.

15 I think the table, while certainly a best

16 practice, evidence-based table certainly is the way

17 to go, is only part of the ball game. We have to

18 teach people how to interpret the data that comes

19 out of that, otherwise we're just doing, as I said,

20 step 3 out of that 5-step process. That's it.

21 DR. STAFFA: Thank you.

22 Dr. Chai, did you want to make a comment

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1 here?

2 DR. CHAI: Yes. I just wanted to build on

3 what Dr. McPherson was asking. This is purposely

4 written a little bit vague because it's a

5 recognition of the current state of things, that

6 maybe there's an overapplication or misapplication

7 of tables for many different purposes.

8 So this is more about can we talk more about

9 what's happening now. What can we say about

10 advancing in this space in terms of science and

11 what is possible?

12 DR. STAFFA: Okay. Thanks.

13 For the record, that was Grace Chai. Thanks

14 for clarifying that, Grace.

15 We started with conversion, but this

16 question is clearly open to the use of these kinds

17 of tables and calculators for other purposes and

18 for other outcomes.

19 Dr. Fine, would you like to add to that?

20 DR. FINE: Sure. I want to preface this by

21 saying I'm not being a gadfly here. I really

22 believe -- and I think it's supported by all the

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1 presentations -- that we recognize the limitations

2 of these tables, as well as the extraordinary

3 variability and standard errors that exists within

4 the populations studied.

5 I think specifically one table that was

6 shown was the transdermal fentanyl data, for

7 instance, where you see mean blood levels for any

8 given dose, but the variability is just

9 extraordinarily high and clinically consequential

10 to the point where, in fact, it turns out the mean

11 levels don't apply to any given individual. In

12 other words, one size does necessarily not fit all;

13 one size fits none. I think what we've been trying

14 to do is -- to put it as a good, close colleague of

15 mine said -- "put a round peg in a square hole."

16 So my comment, really, which I think

17 hopefully triggers some discussion here, is even

18 the term "MME" is a misnomer, based upon some

19 faulty premises, as we talked about earlier at the

20 very beginning of today's discussion. But we have

21 to do something. We have to offer up something,

22 for both research purposes and for population

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1 purpose, to understand epidemiologically what's

2 going on. I appreciate there is a great need for

3 that, but especially a need for individual patient

4 care.

5 I think we've gotten hijacked by the

6 regulatory environment and by policy and political

7 purposes. I won't even begin to get into the

8 opioid litigation, which has driven and perverted

9 so much of what's been going on. And I appreciate

10 comments by Dr. Chidgey and others, who have

11 alluded to those issues, and Penney Cowan, about

12 the fears of prescribers, many of which are really

13 valid fears. It's not paranoia; it is great

14 concern.

15 In any case, what can we do to address these

16 issues but without pretending that this is good

17 science rather than faulty? I'm going to just

18 throw out a thought maybe you're free to chew on,

19 and that is, instead of morphine milligram

20 equivalents, I think what we really should be

21 talking about in a nonclinical world -- that is

22 research, not clinical care -- is experimental

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1 relative potency, because that's all I think we're

2 really trying to figure out here.

3 What is the relative potency in terms of

4 affecting a given efficacy outcome of one chemical

5 versus another, but recognizing that it's all

6 experimental because of the nature of the

7 methodology that got us to these tables in the

8 first place?

9 We have not had large, prospective cohort

10 studies with all the variables that we've talked

11 about. So in the nonclinical research world, it's

12 really about experimental relative potency, and in

13 the clinical-use world -- practices such as mine,

14 where I have to make day-to-day decisions, either

15 in my clinic, in the hospital, and on the

16 palliative care service, and the home-based hospice

17 service -- what do I turn to? How do I teach my

18 colleagues? How do I teach my fellows, residents,

19 et cetera?

20 I need something as a starting point, and

21 we're going to get to further discussion about how

22 to use this practically and safely. But I think

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1 the appropriate language would be an experimentally
2 based or experimentally derived conversion dose,
3 because that's honestly what it is. It's an
4 experimentally derived conversion dose, which it
5 becomes a mean around which there's high degree of
6 variability. So at least I think there would be
7 the more honest descriptor, rather than, quote,
8 "MME." Thank you.

9 DR. STAFFA: Thank you for that comment,
10 Dr. Fine, and for starting the discussion. I think
11 that dovetails very nicely with Dr. McPherson's
12 comment, which is, it's only one piece of a larger
13 consideration that needs to be given; for taking
14 that and then figuring out what else needs to be
15 done. So that experimentally derived language I
16 think kind of does that.

17 But then there's also the issue of having
18 all the different answers that come out of the
19 different calculators. So if folks have comments
20 on what to do there, that would be helpful as well.

21 Dr. Bettinger, I think you were next.

22 DR. BETTINGER: Yes. I'm still here.

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1 This is Jeff Bettinger, pain management
2 pharmacist. I think I'm kind of reiterating what
3 Dr. Fine and Dr. McPherson just alluded to, but I
4 like the idea of maybe even renaming this with a
5 different approach, looking at relative potencies
6 but, again, as we discussed earlier, centering it
7 around a specific clinical endpoint.

8 The majority of these calculators
9 online -- the majority, not every single one of
10 them -- but the majority of them -- I think in my
11 clinical view, as working with a lot of different,
12 again, primary care providers, but as well as pain
13 providers -- use them more as a reference to
14 usually establish some type of conversion or,
15 again, figure out the equal analgesic equivalent.

16 I think, again, where we need to really be
17 careful and mindful is using these relative
18 conversions, whichever standard we use, and then
19 applying it and saying, at this dose, X amount of
20 patients are automatically at risk. Again, the
21 evidence that was used in certain guidance
22 documents that made those recommendations was

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1 extremely weak and extremely poor evidence. It
2 wasn't based off of really robust clinical trial
3 data. And again, we haven't fully studied the
4 impacts of, again, states and third-party payers
5 that have changed their ways centering around
6 specific -MMEs.

7 A lot of times, going back to these
8 calculators, using these types of calculators, I
9 know a lot of presenters had pulled up the CDC
10 conversion calculator itself and noted the severity
11 of the flaws associated with that single
12 calculation when we use it in, I guess, the wrong
13 way or the incorrect thing.

14 So again, I think, as Dr. Fine said, really
15 centering it around a specific clinical endpoint
16 and not using it as an all or nothing approach. If
17 anyone over 90 needs to get lowered down to 90, I
18 think there's bountiful evidence that has shown
19 that is an extremely dangerous approach to utilize,
20 but also thinking about how to standardize these
21 relative potencies. Hopefully that sparks some
22 more discussion here. Thank you.

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1 DR. STAFFA: Thank you.

2 I'd like to just follow up with a question
3 for you. What kinds of clinical endpoints would
4 you suggest? Can you just give a few examples of
5 what you're thinking about in this space?

6 DR. BETTINGER: Absolutely. I'll leave some
7 of this to my epidemiology colleagues, who can
8 probably talk about this at a much more expertise
9 level than I can.

10 I think one of them is overdose data because
11 that to me was the big driver when we were looking
12 at these prescription data and overdose data
13 20 years ago, and kind of seeing how they both
14 paralleled each other. Prescription opioids were
15 going up. Overdose deaths of opioids were going
16 up. Then all of a sudden, prescription opioids are
17 going down and overdose death data is still driving
18 up.

19 So to me, that's where a lot of this fear
20 and a lot of these changes in policies, again, from
21 different organizations and different levels, come
22 from. I think looking at overdose data and just

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1 comparing some of that, specifically how, I think
2 there are probably a number of ways to do it.
3 I think the other approach is, again, let's
4 try to take a look at potential different risk
5 factors, so those clinical endpoints that you were
6 talking about. One of them, which I think of
7 course has to do with overdose is respiratory
8 depression.
9 What is the risk of respiratory depression,
10 or very specific, CO2 accumulation in someone
11 that's been maintained on MS Contin, 45 milligrams
12 twice a day for ten years, versus who was otherwise
13 healthy, doesn't have any respiratory ailments, and
14 doesn't have any other risk factors, versus what is
15 the respiratory risk?
16 What is the CO2 impact or, again, the
17 suppression of our breathing ability? What is that
18 compared to someone who's on IR morphine,
19 15 milligrams twice a day or 3 times a day, a much
20 lower dose, yet they have underlying COPD, on
21 chronic oxygen, with high blood pressure, and has
22 had multiple heart attacks in the past, and

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1 strokes?
2 So I think looking at those very specific
3 clinical endpoints, and maybe there's a way to do
4 it and maybe there's not. But I think that's one
5 way, especially around these MME calculators,
6 talking about the potency of these opioids, again,
7 assessing it and different clinical effects, that's
8 one way we could do it.
9 Again, not saying it would be easy, as
10 Dr. Comer pointed out a few questions ago about the
11 abuse liability clinical endpoint. None of this is
12 easy to look at. But I think it's important to
13 recognize we at least try to start making these
14 distinctions, because, again, the population being
15 affected the most by a lot of these policies, and a
16 lot of these changes in perceptions and
17 comfortability level with opioid prescribing, are
18 chronic pain patients, most of whom do not have
19 substance-use concerns and do not necessarily have
20 respiratory concerns.
21 So again, that's some of the examples I was
22 thinking, but I don't know if that answers your

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1 question wholly, Dr. Staffa.
2 DR. STAFFA: Yes. Yes, it does. Thank you.
3 DR. BETTINGER: Okay. Perfect.
4 DR. STAFFA: Thank you for providing a
5 little bit more detail around that. Thank you very
6 much.
7 DR. BETTINGER: No problem.
8 DR. STAFFA: Dr. Sandbrink, did you want to
9 weigh in here?
10 DR. SANDBRINK: Yes. Friedhelm Sandbrink
11 here, Veterans Health Administration, Washington,
12 D.C.
13 Many have said this very eloquently here
14 already a little bit earlier, but we do need these
15 tools. I think the conversion tables that we have,
16 whether that's a reference table that is being
17 provided as an app or in any other way, I think
18 these tools, among others, are really needed.
19 I think seeing all the different tools out
20 there, it's just a reflection of how important they
21 play as a role in our clinical care. I think the
22 clinicians need these tools. I think we have to be

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1 just a little bit more honest about it, that while
2 there are many out there, we've still kept it
3 relatively simple.
4 We've had these conversion tables. They
5 don't take into account necessarily whether this is
6 for acute or chronic care; whether this is for
7 lower or for higher dosages. Yes, we do make
8 adjustments for different formulations, i.e., PO
9 versus IV, but we presume this to be across the
10 board for all the characteristics an opioid
11 medication has.
12 But we will need probably specific tables
13 for the analgesia, as was mentioned, and then maybe
14 for the ability to prevent the withdrawals, and
15 maybe for the respiratory depression specifically;
16 and those can be separated, and there are better
17 reference tables that may be needed as a backup and
18 at the same time some kind of note that basically
19 comes with all of these conversions that indicates
20 the limitations for what their specific purpose is,
21 for what this is that is being addressed.
22 I think having a gold standard is an idea.

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1 If there's some kind of published official
2 conversion, I think people would love that.
3 Certainly, it comes obviously with risks in regard
4 to is this really the best one or is there an
5 overinterpretation of the value of this and not the
6 recognition of the limitation.
7 But I want to encourage the FDA, as well as
8 others in the federal government, to make sure that
9 we provide this information and these tools out
10 there to the field somehow. Thank you.
11 DR. STAFFA: Thank you, Dr. Sandbrink.
12 You're kind of harkening back to some of the points
13 that Dr. McPherson made, that maybe we're in a zone
14 where we're oversimplifying and that perhaps
15 developing a gold standard table might contribute
16 to that. But maybe the more important thing is
17 maybe we need multiple tables for different
18 outcomes with appropriate citation of limitations,
19 but also the added information of how you interpret
20 those values of what you get out of there and what
21 are the important other factors that will influence
22 your ultimate decision about dose conversion or

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1 rotation. I think those are some very good points
2 that you've brought up.
3 Dr. Comer, would you like to weigh in here?
4 DR. COMER: Yes. I guess to echo what
5 Dr. Sandbrink was just saying, this is what I was
6 trying to convey in my presentation.
7 I am all for using an endpoint like ED50s,
8 for example, to calculate the relative potency of
9 the range of different drugs. I think that's a
10 step in the right direction. But just a word of
11 caution, those ED50s are subject to a whole host of
12 caveats: how intense is the pain; what route of
13 administration is used; what level of physical
14 dependence, if any, the person has. I completely
15 agree with what he was saying. It would be
16 helpful, I think, to have tables like this as long
17 as we include those caveats there.
18 Also, just to echo I think it was
19 Dr. Bettinger who was saying incorporating, as
20 well, in these tables of relative potency not only
21 analgesic responses, but also toxic effects; so
22 this is the dose that produces this level of

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1 respiratory depression, so it's the you have to be
2 careful kind of thing. So you have multiple tables
3 for these kinds of effects that are sort of all
4 interrelated.
5 DR. STAFFA: Right. I think your work
6 really highlighted some of the differences between
7 the analgesia potency and some of these other
8 outcomes, so I think that's really a fair point.
9 Thank you.
10 Dr. Fine, did you have another comment to
11 make here?
12 DR. FINE: Yes, thank you.
13 Dr. Bettinger went into the toxicology and
14 respiratory depressant mode on some of the clinical
15 effects, but I would sort of supplement the list.
16 If you look at most of the reasons -- and this has
17 been pretty well studied by not only myself but
18 many others -- of why do people need to - I'm
19 speaking now specifically about clinical care and
20 switching from one opioid to another, either
21 so-called opioid rotation or conversion. When
22 there's either insufficient analgesia, excessive

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1 adverse effects, or the route of administration
2 needs to be changed, there's a concern about
3 excessive, or tolerance developing, or potentially
4 a hypothesis around hyperalgesia.
5 These are the clinical circumstances that,
6 day to day, an individual who's on a given dose,
7 would potentially need to be switched to another
8 dose, and there are a host of others, but those are
9 sort of the top-of-my-mind lists.
10 The emphasis has always been in the
11 literature -- dating back to when people like
12 myself, and Lynn McPherson, and Lynn Webster, and
13 others who have contributed, Russ Portnoy, and
14 others who have contributed, to studies
15 hypothesizing certain tools and techniques -- to do
16 this safely and effectively. The consideration has
17 always been safety first; that is, you don't want
18 to induce respiratory depression. People can
19 tolerate virtually everything but that. That is
20 obviously the coup de grace.
21 So the methodologies we've used -- and these
22 have been described in papers by I'm sure most of

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1 you are familiar with; Lynn McPherson's written
2 books on this, and I've written much, articles and
3 so forth -- just have not been wholly embraced.
4 And partly is, even if we -- and I completely
5 agree, as was said by Dr. Sandbrink, we need
6 something, so we've relied upon these tables as
7 this is a starting place. Don't overly rely on
8 them, but you need something to guide you. This is
9 the place to start, but people have not gone the
10 next steps. And as Lynn has so forthrightly put,
11 this is only number 3 out of 5 really critical
12 clinical considerations, amongst others.
13 Something Lynn McPherson said yesterday has
14 really stuck with me, which is, if it's too
15 complicated, people won't do it. But that is just
16 a reality that I think we have to live with and
17 acknowledge. So how do we now pragmatically deal
18 with the fact that it is very complicated and
19 people won't do the right thing? If they did, we
20 wouldn't have necessarily had all the problems
21 we've had in the last ten years or so, or more.
22 So to answer these questions with all that

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1 as pretext, the notion of a gold standard -- well,
2 morphine has been around for a long time, so it is
3 a gold standard against which everything else is
4 compared. It's just become a de facto default,
5 whereas we know that, sadly, morphine is a useful
6 drug, but it's also a very dirty drug with M3 and
7 M16 metabolite, and other disposition problems
8 with histamine release. It's versatile in certain
9 ways, but it certainly has its limitations.
10 So it's just odd that that's become the gold
11 standard, though it's a really historic one, but
12 doesn't necessarily make pharmacological or
13 clinical sense. Maybe there is no gold standard
14 per se, but what we do is simply have to have a
15 relative -- as we talk about relative
16 potency -- and relative experimentally based
17 conversions where we don't have good data. Because
18 let's face it; almost all the drugs we've been
19 talking about have not been directly compared in
20 multidose, crossover studies, with no less
21 different formulations of morphine to these other
22 drugs. So it's quite specious to use this as a

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1 gold standard.
2 The second point, then, is really an
3 introduction to a whole new idea. I brought this
4 up yesterday, I guess prematurely, but I was really
5 trying to maybe get some thoughts about this from
6 others, but it lends itself more to discussion than
7 it did to the clarifying questions yesterday.
8 That has to do with, really, recreating a
9 whole new tool that doesn't require new science; it
10 just requires use of skills and expertise that we
11 currently have and applying them to this problem,
12 this complex problem, like we have other complex
13 problem-solving in other areas of medicine like
14 ventilator settings in severe respiratory distress
15 syndrome, or dosimetry in radiation therapy.
16 We don't just sort of scratch our heads,
17 look at a little table, and then push a button, and
18 then reductionistically say, okay, let's do it, and
19 then let's add a little, subtract a little, and, oh
20 my gosh, I forgot this variable or that variable.
21 It's just beyond what human beings - even
22 well-educated, well-intended health

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1 professionals -- can do. There's just too much
2 variability complexity.
3 So I would suggest at this point that we
4 move towards development of a more thoughtful tool,
5 one that incorporates and demands input of
6 variables, to the extent we have them, to get to a
7 starting point where we start then having
8 experimentally induced or experimentally derived
9 conversion doses.
10 What I'm talking about, of course, is
11 decision support, where instead of just looking at
12 a tool and doing our calculations by hand, or
13 mentally, or on paper, basically, it's a
14 plug-and-play device. I don't want to simplify by
15 saying it's an app, but it ultimately would become
16 a computer-driven, decision-support tool. That's
17 what we use in ICUs, it's what we use in radiation
18 therapy, and what we use in a host of other
19 domains. Why not in this area of healthcare?
20 Thank you.
21 DR. STAFFA: And thank you, Dr. Fine, for
22 bringing that up again. You'll notice I have

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1 flipped the question to question 5, because I think
2 when we mentioned algorithm definitions, I think
3 decision support can provide both qualitative or
4 quantitative, or both, types of tools to help with
5 this.
6 So again, I kind of think of questions 4 and
7 5 as going together. So if folks have comments on
8 that, I would encourage you to chime in on that
9 point, where you see the utility there, but I don't
10 want to preclude folks from making points about
11 question 4 as well.
12 Dr. Zhang, did you have your hand up? Would
13 you like to make a comment?
14 DR. ZHANG: Yes. Thank you. This is Kun
15 Zhang from CDC. First of all, I agree with what
16 Dr. Sandbrink just commented. What I want to see
17 is, again, a data point. I want to remind all of
18 us, in 2019, there were about 1 million prescribers
19 nationwide who wrote at least one opioid
20 prescription.
21 The reason I say this number is I think
22 there is a huge need for some type of tool for

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1 these 1 million providers. I think we need more
2 research, understanding what is the need and what
3 kind of tool can better help them. What we
4 currently have, is that sufficient, or how can we
5 improve the resources and tools provided for these
6 large number of providers so that they can use in
7 their clinical practice, and as a result, of
8 course, helping patients and making sure of safe
9 prescribing and better outcomes.
10 That's my comment. Thank you.
11 DR. STAFFA: Thank you, Dr. Zhang.
12 Dr. McPherson, would you like to make
13 another comment?
14 DR. MCPHERSON: Yes. Thank you. Lynn
15 McPherson again. I want to get back to what
16 Dr. Fine was just saying. I completely agree.
17 This is very complicated. I mean, it's not
18 rocket science, but it's pretty darn complicated.
19 I think we have to consider MMEs for the
20 medical/legal opioid crisis conversation separate
21 from the patient care conversation, and I know they
22 certainly cross paths there. But in caring for

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1 patients and doing calculations and conversions,
2 don't even bring up the MME stuff; just call it
3 equianalgesic dosing.
4 But I agree with Dr. Fine. I do still think
5 we need a super awesome equivalency chart that is
6 constructed on the very, very best evidence we
7 have, crossover trials, steady state that shows
8 bidirectionality, because you can't just throw
9 people out into the woods and expect they're going
10 to find their way home by themselves.
11 But I do think, I don't know, maybe the next
12 time I update that bloody book, I'll make it more
13 of a critical thinking process, as Dr. Fine was
14 just saying, where you take people by the hand and
15 go step, by step, by step. And one of those steps
16 is referring to the best-evidence chart; so an
17 explicit critical thinking process.
18 Now, the MME thing, I think imposing these
19 limits, it's almost become like a dirty word in a
20 way. And yes, I do think it's had some inroads and
21 maybe ruling out some crazy prescribing of opioids,
22 but I don't think it's really met the mark of what

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1 we were hoping it would do, which is to turn around
2 the opioid crisis. I don't think it's really done
3 that. And I think we've seen an array of impact on
4 patient care by imposing these MMEs.
5 So I think the whole MME conversation -- and
6 as Dr. Dasgupta just pointed out, there are 47 ways
7 to calculate the MME -- this also needs to be a
8 critical thinking process, but a different one from
9 the direct patient care because my patient is
10 vomiting and he can't swallow MS Contin anymore.
11 So I don't think we can throw the baby out
12 with the bathwater, but I think these are almost
13 two separate issues, and they're two separate
14 critical thinking processes. Thank you.
15 DR. STAFFA: Thank you very much for those
16 thoughts.
17 Ms. Cowan, would you like to add thoughts
18 here?
19 MS. COWAN: I'm sorry. Yes. I'm just
20 trying to play around with this thing and forgot
21 what I wanted to say.
22 But if we go with all of the things that

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1 were just said, I think we also have to remember
2 that there's more to pain management than just the
3 right medication. So I agree with everything that
4 was said, but I think we need to take the next step
5 and make sure that we -- like she said, you can't
6 just throw them in the woods and find a way, but we
7 can give them a map. We can give them a map and
8 teach them how to get their way back, in addition
9 to.

10 I think a lot of that needs to go to
11 professional education. We can't just give them a
12 chart and say use this, and then we go back to just
13 prescribing medication and not looking at all the
14 other components of pain management.

15 So while this is really important and they
16 need to know how to do it, I think without that
17 professional education on the broad base of pain
18 management and all of those components, that
19 balanced approach, we're missing the mark. So I
20 just, again, wanted to caution you that provider
21 education is one of the missing pieces right now
22 when it comes to treating people who live with

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1 pain. Thank you.

2 DR. STAFFA: Thank you for bringing us back
3 to that. That's a great point, that we need to
4 remember this is just one piece of a much larger
5 picture.

6 Dr. Comer, would you like to weigh in?

7 DR. COMER: I would, just to offer a
8 suggestion. This is Sandy Comer from Columbia
9 University.

10 In listening to all of these presentations
11 and the discussions over the last two days, I would
12 just really urge the FDA to create a working group,
13 really, to talk about how to develop these kinds of
14 tables, bringing together a lot of the people who
15 are here today, and also pull in people who've
16 spent their careers, really, studying these kinds
17 of questions and issues from the preclinical arena.

18 I think Dr. McCann is really an excellent
19 resource, and he should be included in the
20 discussions for sure. But there are also really
21 excellent preclinical researchers who have thought
22 about a lot of these issues who could bring a lot

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1 of insight to the table in terms of these kinds of
2 discussions.

3 DR. STAFFA: Thank you. Those are great
4 thoughts. And yes, now that we have kind of pulled
5 this group together, I think you're right. It
6 might make a lot of sense to turn this into a more
7 formal effort. But these discussions help us to
8 define what the mandate for such a working group
9 might be, so this is very helpful.

10 Other thoughts on this, this idea
11 of -- again, what I'm hearing a lot, too, here is
12 the need for more education around the concepts of
13 pain management, which I know you heard from
14 Dr. O'Donnell yesterday, that part of our opioid
15 analgesic REMS is that education is provided,
16 again, not just about opioids as part of pain
17 management but the larger picture of pain
18 management. So we've made some efforts in that
19 direction, but perhaps there need to be more.

20 I'm also hearing the need for education
21 around these kinds of MME tables, whether they're
22 targeted toward providing conversion factors

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1 related to analgesic potency or these other
2 outcomes we've discussed if we had multiple tables,
3 but education on the whole package of what role
4 that plays -- [inaudible -- audio gap] -- of either
5 initiating, or converting patients, or rotating
6 patients on opioid therapy, and then perhaps
7 another educational effort on the challenges that I
8 think Dr. Dasgupta pointed out, of how we might be
9 using big data that don't have a lot of granular
10 clinical detail to evaluate these, or to identify
11 people and some of the challenges there; some of
12 the education around, again, not oversimplifying,
13 which I heard Dr. Sandbrink saying --
14 [inaudible] -- among the busiest these days, but
15 this idea that this oversimplification -- clearly
16 from what we've heard the last two days -- is not
17 supported necessarily by science; so how do we
18 infuse the science in there.

19 Dr. Fine, did you want to weigh in again?

20 DR. FINE: Yes, just a reminder about the
21 history of things again. Sadly, but truly, any and
22 all things attached or funded - even with various

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1 types of firewalls connected to them, or
2 independent grants, or no-strings-attached grants,
3 including the risk management programs and
4 mitigation strategies within FDA that are funded by
5 pharmaceutical companies -- have been met not only
6 with skepticism, but unfortunately with such levels
7 of cynicism that they've fueled a lot of what's
8 going on that has been very negative in terms of an
9 impact on patients living with debilitating pain;
10 so a lot of the comments we heard yesterday and a
11 lot of the reminders that we've had from Penney
12 Cowan.
13 Even though I appreciate the efforts of the
14 FDA, I do recall the beginnings of this when it
15 went from RiskMAPs to REMS, well over 10-12 years
16 ago, and conversations that said, look, this is
17 probably not going to go well as long as it's
18 funded by drug companies for one reason or another,
19 and sure enough, that's where we find ourselves.
20 The narrative has been hijacked. Anything and
21 everything attached to -- anything even remotely
22 related to -- the pharmaceutical industry, can be

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1 construed as somehow perverted, or disingenuous, or
2 whatever.
3 So with that said, if we're not going to end
4 up with a pain institute that's publicly funded at
5 NIH, and I still hope we will have one, I would
6 hope that FDA would at least reconsider how to get
7 involved in more global pain education that's more
8 comprehensive.
9 It's not the FDA's job, but a lot of this is
10 politicking. It's how to convince the insurance
11 industry they ought to actually cover
12 interdisciplinary comprehensive pain care; that the
13 kinds of research that we've been talking about is
14 actually funded; that CDC gets involved in not just
15 naming things an opioid epidemic but actually gets
16 to more of the main point that we have problematic
17 opioid use, and not just because it may have been
18 driven in certain ways by prescription opioids, but
19 the root causes for that have not been adequately
20 explored, and we still have not done much to
21 improve the lives of people living with
22 debilitating pain, so we have a pain epidemic and

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1 how we deal with the overlap of these things.
2 In discussing solutions, not only do we need
3 a specific tool, because if we go back,
4 again -- and I know, I'm sorry, this is a lengthy
5 commentary here, but their history is so important.
6 If we go back to the inception of all this, I don't
7 remember anybody ever standing up and saying
8 opioids are the panacea for anything and everything
9 when a person says this hurts.
10 What was talked about, and educated, and
11 taught throughout at least my entire career was, if
12 and when such time comes when opioids may be
13 indicated -- may be indicated -- for part and
14 parcel of comprehensive pain treatment, we ought to
15 know how to use that tool safely and effectively,
16 and here's how you do it.
17 One tool, a tool that talks about relative
18 analgesic equivalency and is honest about it, and
19 says these are experimental relative potencies, or
20 currently derived-based conversion doses, what's
21 the tool to do it? We've talked about that as
22 maybe decision support that can be computer driven

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1 and fitted on everybody's smartphone.
2 Yes, it is only one component, but if we
3 talk about larger pain education to drive this
4 forward, once again, we need a new paradigm, and
5 one that's not necessarily attached to
6 pharmaceutical dollars.
7 DR. STAFFA: Thank you, Dr. Fine. I think
8 you've made some very good points about pain
9 management and how opioids certainly should not be
10 the sole focus of pain management.
11 I would encourage folks, as we've alluded to
12 yesterday, the FDA developed a blueprint to provide
13 the basis for that continuing education type
14 training. And it's posted on our website, so folks
15 can take a look and see. And obviously we're
16 always interested in comments of how that could be
17 improved, so happy to hear about that.
18 Dr. Chai, did you want to ask a clarifying
19 question or make a point?
20 DR. CHAI: Yes. I just wanted to build upon
21 the comments that have been made and see if we can
22 elicit more response in that direction.

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1 This is really a chance for us to brainstorm
2 different strategies that can be taken. We heard
3 the suggestion from Dr. Comer, which is great,
4 about a more formal work group. And what I also
5 heard from Dr. Fine - I'm not sure if this was
6 what you intended, but maybe consideration of
7 different expertise that could help inform a formal
8 work group such as decision-support analysts, like
9 people who that's the science, that's their
10 background, that's their expertise. We definitely
11 heard about the important role of pharmacists and
12 that type of expertise to inform such a development
13 of something.

14 This is a lot of great thinking and
15 solutions. We definitely heard suggestions for who
16 should undertake this. NIH has been mentioned.
17 FDA has been mentioned. But I just want to
18 encourage more brainstorming in that aspect,
19 because this is our time to just see what everyone
20 else knows, external experts like yourself.

21 DR. STAFFA: Thank you, Dr. Chai.
22 I'm going to move to the next question. And

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1 again, this is continuing our conversation about
2 what other areas do we think need to be looked
3 into, other areas that this working group could be
4 considering, or that some of our federal agencies
5 could be considering and figuring out ways to
6 support work in this area.

7 We've talked about a number of different
8 areas involving studies around patients with
9 chronic pain and trying to develop other types of
10 tables relating to calculating MMEs, but perhaps
11 that's not the right name for it. Perhaps we
12 should be thinking about it in other ways, like an
13 experimental -- there was a term. Hold on. I
14 wrote it down; "experimental potency" as a starting
15 point for looking at whether and when a patient
16 should be started [inaudible – audio gap].

17 Are there other gaps? We haven't really
18 talked very much about any nonclinical work that
19 folks think needs to be done in this space.
20 Anything that folks want to put forward there that
21 might be part of a research agenda that is just
22 painfully needing to be done, either before or

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1 perhaps even simultaneously, with some of the
2 clinical work we've talked about?

3 Dr. Comer, did you want to make a comment?

4 DR. COMER: Yes. I think this is a really
5 interesting question that you're posing here about
6 how novel opioids or non-opioids -- well, actually,
7 maybe I just misread it. It was thinking, would it
8 be helpful, useful, for the clinicians in the group
9 to have a table that would convert equianalgesic
10 doses from not just morphine to oxycodone, but from
11 morphine to a non-opioid medication?

12 It just occurred to me that that would be a
13 different way of thinking of things and how to use
14 a non-opioid medication that would potentially
15 provide the same level of analgesic response.

16 DR. STAFFA: Right. That's a great
17 question, and also thinking about some of the
18 opioids that don't necessarily fit into the current
19 tables or calculations; do we need to be thinking
20 about is there any research or anything that needs
21 to be done to try to provide better tools across
22 the board for pain management?

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1 Dr. Fine, did you want to weigh in?

2 DR. FINE: Yes. It's a really interesting
3 idea, but I'm just sort of swooning a little bit
4 about what kind of model. For instance, I'm
5 thinking about two very different clinical
6 scenarios.

7 For instance, take an acute pain condition
8 like renal colic, where essentially 50 milligrams
9 of intravenous ketorolac may provide very
10 high-quality pain relief, whereas you can infuse a
11 very high dose, almost to the point of apneic
12 doses, of fentanyl with only modest reduction in
13 patient-perceived pain because the mechanism of
14 action is different, and the way pain relief occurs
15 as a result of that is different.

16 The other I guess is a similar issue, for
17 instance, in metastatic bone pain, where
18 corticosteroid or non-steroidal anti-inflammatory
19 drugs may be highly effective and, again, very high
20 doses of opioids may only modestly reduce pain
21 perception.

22 So I'm not sure how to cross pharmacological

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1 classes in the same way as an interclass effort at
2 an experimentally based conversion dose, comparing
3 apples and apples. But I think your question,
4 actually in a reverse way, begs should we ever be
5 even comparing pure mu opioid agonists to more
6 complex agonists, or partial agonists, or those
7 drugs with certain adrenergic or NMDA-receptor
8 actions, and is that even a manageable thing to do
9 at this point in time for similar reasons, because
10 the mechanisms of action are different. Thank you.
11 DR. STAFFA: Thank you for that comment. I
12 think that does raise questions because, again, it
13 gets into some of these other outcomes along with
14 analgesia, how you convert patients or perhaps add
15 other agents so that you're not increasing the risk
16 of respiratory depression but perhaps increasing
17 the analgesia, and that really depends on the
18 indication and the type of pain you're treating, I
19 think, as you mentioned.
20 I don't know if these tables really play a
21 role there, but maybe as part of this algorithm or
22 this broader consideration of once you go through

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1 and look at the table and look at what you're doing
2 there, to be considering other drugs. I think
3 Dr. McPherson gave some good examples of how folks
4 often don't think about that, but that perhaps that
5 could be built in, in terms of further research,
6 knowledge, and understanding of how other therapies
7 complement opioid therapy or other things to
8 consider.
9 Again, but it's part of that whole
10 education, that that calculation is just part of
11 the entire care of the patient or, again, looking
12 at the patient situation to determine the risk.
13 Dr. Comer, did you want to make a comment?
14 DR. COMER: Yes, just to follow up on this
15 basic question about gaps in the science, one thing
16 that has been really exciting in the field of
17 treatment of opioid-use disorders have been the
18 development of these sustained-release formulations
19 on the order of a week or a month for reducing the
20 illicit use of opioids.
21 You can imagine, actually, that some of
22 these long lasting opioids might also have some

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1 applications in treating pain. I think that's
2 something that we haven't really explored at all
3 yet. So that's definitely a gap that we could
4 think about, because there's sustained-release
5 buprenorphine, for example. There are a couple of
6 different formulations, one that's just been
7 approved and another that's about to be approved.
8 DR. STAFFA: Dr. Bettinger, would you like
9 to jump in here?
10 DR. BETTINGER: I didn't know if Dr. Fine
11 had his hand raised before me. I can let him go if
12 he --
13 DR. STAFFA: Okay.
14 Dr. Fine, did you want to make a follow-up
15 comment, and then we'll go to Dr. Bettinger?
16 DR. FINE: Oh, Jeff, go ahead, please. Go
17 ahead, please.
18 DR. STAFFA: We'll come back to you after,
19 then, Dr. Fine. You'll be first up after
20 Dr. Bettinger.
21 Go ahead.
22 DR. BETTINGER: Okay. Thank you, Dr. Fine.

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1 I was going to comment to Dr. Comer's
2 original idea, which I agree with. I think it's
3 really intriguing, even in the sense of at least it
4 would get clinicians to think about, again, what is
5 the goal of this MME conversion. We're not just
6 kind of blindly following these numbers and
7 conversion factors where we're kind of critically
8 thinking -- going back to Dr. McPherson -- about
9 these in those different contexts.
10 I also really like the idea of looking
11 at -- as Dr. Comer said - different, long-acting,
12 and the prospect of sustained-release opioids,
13 especially for patients where maybe their pain is
14 relatively managed, or they're using IR, and we
15 know about the peaks and troughs, and they have to
16 take it multiple times a day, and there are periods
17 of not so great relief, looking into more
18 extended-release opioids.
19 I know there have been some trials out there
20 that have not necessarily shown significantly
21 improved outcomes in terms of pain relative to
22 short-acting, but I wonder if we, again, just

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1 continue looking at those differences; and even
2 things like more long-acting opioids, ones like
3 Dr. Comer was saying, the injectable buprenorphine
4 that will last in the system for a while from a
5 pain perspective.
6 I think all of those are really good ideas
7 to look at, again, harkening all this back to the
8 education and what does that look like in terms of
9 educating our clinicians, who are the ones kind of
10 left to figure this out. Is it making them all
11 required to read Dr. McPherson short text books?
12 Maybe that's what we need to do.
13 I think maybe grassroots campaigns could be
14 an attempt to, again, have some of these
15 conversations at the clinician level, because I
16 think creating work groups and guidance documents
17 are always going to be great, but I think we should
18 be realistic. For the vast majority of all
19 practitioners, the majority, they're going to kind
20 of do a quick look. They're not going to really
21 get into depth with what's going on.
22 I think figuring out ways we can do some

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1 more grassroots campaigning -- again, as Dr. Fine
2 said -- without necessarily the involvement with
3 pharmaceutical companies and industry, which,
4 again, from a funding perspective, I'm not exactly
5 sure what the answer is. But that could be another
6 route, too. Thank you.
7 DR. STAFFA: Thank you, for your comment.
8 Dr. Fine, did you want to jump back in here?
9 DR. FINE: Yes. There's something that sort
10 of was clawing at me. I took so many notes on
11 yesterday and today that I've been digging through
12 so I wouldn't waste all your time sifting through
13 stuff.
14 One issue that we haven't really covered
15 that I would hate to conclude today without at
16 least thinking about a little bit, even though this
17 is not a discussion about healthcare financing, God
18 forbid, but it enters into everything -- one of the
19 things that I think would be very useful for this
20 group to at least weigh in on and at least make
21 note of, and perhaps with a relatively large font
22 underlined and bold is, when is it clinically

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1 indicated or what kind of consensus could be
2 developed out of groupthink to do so when
3 monitoring is a priority or is indicated in dose
4 conversion?
5 Whether it's from an opioid to another
6 opioid, or from an opioid to a non-opioid, or
7 adding a non-opioid or vice versa, when is
8 monitoring a critical part of clinical care rather
9 than writing a prescription, doing a little
10 counseling, and sending somebody home with a few
11 notes and hoping for the best?
12 I suspect that if there was a guideline for
13 that or some guidance about that, it would create
14 great comfort for clinicians in a host of settings
15 but also save lives.
16 I just want to add a clinical case in terms
17 of that discussion that Dr. Comer brought up and I
18 talked about, considerations where a small dose of
19 NSAIDs, relatively speaking, or corticosteroids
20 might substitute for a large dose of opioid. But I
21 would also consider the circumstance where a
22 patient almost has a significant or severe pain

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1 disorder that is amenable to some degree of opioid
2 therapy but is not adequately treated, and still
3 there's indication for either interventional or
4 pharmacological care.
5 For instance, consider the circumstance of
6 somebody with widespread metastases in the advance
7 stages of disease, who is bedridden, can't move
8 because of severe pain, is on a relatively high
9 dose of opioid, corticosteroid, and NSAID, and
10 nothing else is touching their pain; and they can't
11 communicate, and they're becoming agitated or
12 delirious from metabolites of whatever drugs
13 they're on.
14 For instance, in my own practice, under
15 circumstances like this, a very subanesthetic dose
16 of ketamine, a low-dose ketamine infusion, might
17 obviate the need for almost all opioid and allow a
18 clear sensorium in the person actually to function,
19 at least through the remainder of their life. But
20 if you don't drastically reduce the opioid dose at
21 the time of using a very small
22 subanesthetic -- again, a dose of ketamine, like

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1 0.1 milligram per kilogram -- they will stop
2 breathing because the motivation to breathe, the
3 respiratory drive has been so much motivated by
4 pain or by nociception.
5 These are complex considerations and maybe
6 they're one-offs clinically, but unless we think
7 about this in these kinds of comprehensive ways,
8 when is monitoring required; how do we really
9 accentuate safety; how we do go from one drug to
10 another or intraclass pure opioid agonist or pure
11 opioid agonist; how do we actually take the very
12 limited data we have now about converting from pure
13 agonist to, say, partial agonist like buprenorphine
14 and do that without instigating either acute
15 abstinence but also psychologically get people
16 through this transition? What are the principles
17 of practice that would support those kinds of safe
18 transitions?
19 This is a larger discussion, but I thought I
20 would at least get them onto the record. So thank
21 you very much again. This is Perry Fine.
22 DR. STAFFA: Thank you, Dr. Fine.

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1 Dr. Comer, did you want to make a comment
2 about this area?
3 DR. COMER: Yes, just a follow-up. Again,
4 Sandy Comer from Columbia University.
5 Just to follow on that point that Dr. Fine
6 was making about the risk of respiratory
7 depression, I think another gap in the science that
8 we have with regard to pain is how to mitigate the
9 risk of overdose in this population.
10 We have good data from the field of
11 addiction, where we know that if patients are
12 maintained on medications, like methadone or
13 buprenorphine -- naltrexone obviously is not a
14 viable option here -- the risk of overdose goes
15 down. So are there certain types of medications
16 that would be helpful in this regard?
17 People who are on short-acting opioids for
18 pain might have a higher risk, people who are on
19 higher doses, but if they had a baseline of
20 methadone or buprenorphine as their primary pain
21 medication, would the risk decline, basically?
22 That was just my suggestion for a gap.

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1 DR. STAFFA: Thank you. I think that's a
2 very relevant thought.
3 Okay. I'm going to move to the last
4 question. You guys have been great, but we're
5 getting to the end of our time, and I want to make
6 sure we have folks weigh in.
7 What I was hoping is that if you've had a
8 chance to think about all this -- and we've talked
9 about a lot of different areas -- I think we have a
10 lot of things to go back and discuss about forming
11 perhaps a working group around this, different
12 topics for research agenda, and that's going to be
13 really helpful to us.
14 But I'd like to ask if everybody on the
15 panel could weigh in and at least let us
16 know -- and again, the folks outside of FDA because
17 this is our unique chance to hear from you -- if
18 you had to pick one thing that you thought was the
19 most important thing for us to focus on or
20 prioritize in terms of a gap, whether it's an area
21 of research or the education, what one thing do you
22 think is the most important thing for us to start

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1 with or what group of things? But you can't take
2 everything as a group of things. I'm not going to
3 let you do that.
4 It will help us really make sure that we put
5 our efforts in the direction that folks think are
6 really the most important at this point in time.
7 We are very committed, this working group at FDA
8 and with our federal partners, for trying to
9 improve the science in this area, so we'd love to
10 hear what your thoughts are.
11 Dr. Fine, you seem to be the brave one that
12 wants to go first. Go for it.
13 DR. FINE: I've lost all pride in my old
14 age; the years have grounded me down. The priority
15 I would like to see would be a decision-support
16 smart tool that guides critical thinking for
17 purposes of safety, as well as efficacy, when it is
18 determined that opioids are indicated or continue
19 to be indicated.
20 DR. STAFFA: And I'm assuming that's a tool
21 that's been developed and validated, so it has good
22 science behind it, right?

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1 DR. FINE: Well, that's what needs to be
2 developed.
3 DR. STAFFA: Inherent. Okay. Thank you
4 very much.
5 Dr. Chidgey?
6 DR. CHIDGEY: Yes. I think really getting
7 down to the goal of what we're looking at within
8 MME and designing studies that really try to assess
9 that goal, whether it be analgesia, whether it be
10 risk of overdose, because we're just using MME for
11 a lot of different things, and we don't have data
12 to support most of what we're using it for. Thank
13 you.
14 DR. STAFFA: Thank you.
15 Dr. McPherson?
16 DR. MCPHERSON: Yes. I typed into the
17 chatbox. And this might be a little bit Star Trek
18 or make you go blind in your good eye, but there's
19 an emerging body of literature talking about opioid
20 utility, which is based on economic literature,
21 where you look at benefit minus risk.
22 So we're looking at analgesic effects, the

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1 gain, which is the good side, minus adverse
2 effects, notably respiratory depression. Some
3 drugs are a better bet, some opioids, from a
4 utility perspective versus others. I think it
5 probably is a big ask to come up with a utility
6 equivalent chart, but I think that certainly is a
7 consideration worthy of discussion. That's it.
8 DR. STAFFA: Thank you. That's an
9 intriguing thought. We've actually learned a lot
10 from our colleagues in the economic space. They
11 often develop methods that epidemiologists and
12 others find very helpful, so I think that's a great
13 suggestion.
14 Ms. Cowan, would you like to weigh in here
15 on priorities?
16 MS. COWAN: Yes. Penney Cowan. I was
17 thinking -- and I've been thinking about this for a
18 while -- we're talking, and we always tend to talk
19 to some of the top people. But I was thinking,
20 wouldn't it be interesting to actually work with
21 the different academics, the family practitioners,
22 the nurse practitioners, the American Pharmacists

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1 Association, all of those, and actually do surveys
2 and ask them some of these same questions, and get
3 some feedback from real-life experience from
4 practitioners and what are the issues that they're
5 dealing with.
6 Then perhaps even do one for people with
7 pain, and ask them -- though I know we did the one
8 on access to care right after the CDC guidelines
9 came out, but let's ask those questions of people
10 who are on the front lines and actually doing this
11 and struggling, to understand what is it that they
12 need and what would be most helpful to them.
13 DR. STAFFA: Thank you. That's a great
14 suggestion. Thank you very much.
15 Other comments about what our top priorities
16 should be in this area for research, education, and
17 efforts to clarify?
18 Dr. Dasgupta, I was hoping you would weigh
19 in. Go ahead.
20 DR. DASGUPTA: I want to say epi methods,
21 but that's always a given. It's really hard to get
22 epi methods more funded, and I appreciate FDA

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1 support of this project and others.
2 My insight from population science is that
3 we don't really have a good mental model of why
4 physicians prescribe opioids and other pain
5 management modalities and the decision-making
6 process on the ground. In clinical psychology,
7 there's a whole lot of existing work on why certain
8 behaviors of certain groups can be explained, and I
9 think bringing some of that and qualitative work
10 surveys - I think some of that work is actually not
11 as qualitative but is based on doing real-world
12 experiments and understanding the mental constructs
13 that go into the prescribing decision.
14 The best way to improve epidemiology studies
15 is to improve the exposure, to improve how we
16 classify why someone is getting prescribed. So I
17 think doing some of that leg work within clinical
18 psychology frameworks of experimental design would
19 have a lot of potential.
20 DR. STAFFA: Thank you. Can you also just
21 say a bit about where you see the priorities and,
22 again, using big data in this space? Do you see

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1 any way to improve the situation that you
2 described?
3 DR. DASGUPTA: Yes. I think on a practical
4 level, there are a lot of software vendors, and
5 whether this is something baked into Epic or on a
6 PDMP dashboard, or something that's even like an
7 in-clinic based tool, I think the definitions
8 really have to be standard if we're going to
9 continue to use them.
10 As much as I'd like to say more money for
11 basic theory research, what I think actually is
12 needed right now is harmonization. A lot of times
13 those software vendors write out how they're
14 calculating these things in code, and then that
15 code becomes proprietary, so having a common code
16 base that's available across different platforms.
17 There are a lot of logistical things we can
18 do, so at least get to standardized and to bake in
19 some of the broader clinical decisions and not just
20 rely on the number.
21 DR. STAFFA: Thank you. Thank you very much
22 for your efforts in that space.

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1 Dr. Zhang?
2 DR. ZHANG: Thank you. This is Kun Zhang
3 from CDC.
4 Dr. Staffa, I want to add a point you made,
5 which is education. If you asked me to choose, I
6 would emphasize that, education for those providers
7 and patients. As I mentioned, as of 2019, there
8 were about 1 million prescribers of opioids. So
9 that's my comment.
10 DR. STAFFA: Thank you. Thank you for
11 weighing in.
12 Dr. Sandbrink, I think you're the sole
13 survivor of our VA participants. Any comments or
14 prioritizations here?
15 DR. SANDBRINK: Yes. Friedhelm Sandbrink,
16 Veterans Administration, Washington, D.C.
17 Thank you. I really feel that rather than
18 me commenting right now on research, I feel the
19 immediate need is in many ways educating the
20 community, and that probably means also the
21 legislators, about the limitations of what we have
22 been doing in regard to MMEs.

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1 I think we really have to step back and say,
2 yes, research is needed in regard to specifically
3 what is the appropriate application of MME levels
4 and the specifics that we all discussed already,
5 but we also, I think, need to clarify at this point
6 what are the limitations. I think people across
7 the board need to be educated about that in many
8 ways so that this currently ongoing
9 misinterpretation or misperception is being
10 addressed. So maybe that's just an encouragement
11 in that regard.
12 I really feel like it's very hard to develop
13 these decision-support tools. We are trying to do
14 it in the Veterans Health Administration and among
15 others, that takes not only the medication factors
16 into account, but then even more complicated is the
17 patient factors because the risks and the benefits
18 depend obviously on the prescription, on the
19 medication, on the drug, on the formulation, how
20 it's being administered; but just as much, or
21 probably more, at least in regard to long-term
22 risk, on the patient characteristics.

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1 So we have our decision-support tool that we
2 provide to our providers, at least in regard to
3 risk assessment; our certification tool for opioid
4 risk mitigation that allows an assessment using
5 predictive analytics in regard to an assessment of
6 risks, including for patients who are maybe not on
7 medication yet but are being considered for opioid
8 medication and takes the MME levels into account
9 and that has three tiers in that regard.
10 So we are on the way, but we also realize
11 that the patient factors are so very much
12 important, and I think we should never forget that.
13 Thank you.
14 DR. STAFFA: Thank you so much for pointing
15 that out.
16 Dr. Chidgey, did you have another comment?
17 (No response.)
18 DR. STAFFA: Dr. Chidgey, your hand is not
19 raised, but did you have another comment? I
20 thought I saw your hand up.
21 DR. CHIDGEY: I forgot to take it off. I
22 apologize.

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1 DR. STAFFA: No problem; no problem at all.
2 I'm wondering if our colleagues from NIDA
3 have any thoughts or closing comments on
4 prioritizing the research in this area. Anything
5 that comes to mind from either Dr. McCann or
6 Dr. White from the conversation you've heard?
7 DR. McCANN: Yes. This is Dave McCann. I
8 have to say this might be an unexpected response
9 from NIDA because it's not really research related.
10 But I listened to all the presentations yesterday,
11 and we've talked, just in the past few minutes,
12 about improving training of providers.
13 Jeff Fudin yesterday mentioned the problem
14 that pharmacists are not regarded as providers and
15 can't bill for time when they work on something
16 like this. That really does seem like a critical
17 issue to look at because they're already some of
18 the best trained folks out there.
19 DR. WHITE: This is Dave White in NIDA as
20 well. In listening the last couple of days, it's
21 been very edifying to me in this topic in general.
22 It doesn't necessarily pertain to substance-use

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1 disorders, but I keep thinking about demographics
2 and the research that needs to be done regarding
3 what the indication is for these -MMEs.
4 Dr. McPherson has touched upon it and other
5 speakers as well. We really need to start to drill
6 into this topic and decide or determine where we're
7 going with the MMEs and how they're being used.
8 That's just my personal perspective from this.
9 DR. STAFFA: Thank you very much, Dr. White.
10 Dr. Babalonis, did you want to chime in?
11 (No response.)
12 DR. STAFFA: Dr. Babalonis, I think you're
13 still on mute.
14 DR. BABALONIS: Hello?
15 DR. STAFFA: Yes, we can hear you. Go
16 ahead.
17 DR. BABALONIS: Okay. Thank you.
18 I know Dr. Comer had mentioned a working
19 group, and I thought that was a really good idea.
20 I also thought a good idea would be not necessarily
21 a white paper but maybe a review paper of some of
22 the topics that have been discussed over the course

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1 of this meeting, because as someone who works in
2 the field, I wasn't aware of most of what was going
3 on and how many limitations there were to what
4 we're talking about.
5 Just Dr. Dasgupta's presentation alone about
6 how flawed the calculations are, I don't know if we
7 could put together something like a review paper
8 with the panelists that just described all these
9 limitations, and then some future directions as one
10 starting point.
11 DR. STAFFA: Alright. Thank you for the
12 suggestion. That's a good idea.
13 Dr. Fine, did you have another idea you
14 wanted to share?
15 DR. FINE: Yes. I wanted to pick up on this
16 little note that Dr. McPherson wrote. She said,
17 "If you put together a work group, they should
18 explore the concept of opioid utility," and maybe
19 this also goes along with Dr. Babalonis' last
20 comment.
21 There's a very potent, powerful, and
22 pervasive narrative over the last, say, 5 to

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1 10 years, certainly since the national opioid
2 litigation began, that there is no utility to
3 opioids. That there is no safe dose and there is
4 no efficacious dose other than for maybe a few
5 days, at most, after a severe injury or surgery, or
6 in the last few days of life, whenever that might
7 be.
8 Clearly, the fact that FDA is sponsoring
9 this workshop and FDA has approved drugs when
10 indicated for pain that cannot be controlled in
11 other ways, says that in fact there is utility,
12 implied utility. We certainly heard that from our
13 public commentators yesterday, as well as the
14 millions of patients that we know are using opioids
15 on a regular basis as part of a plan of care for
16 managing their pain, and doing so effectively and
17 safely.
18 So I'm wondering at this point -- along the
19 lines of those discussants, Dr. Comer,
20 Dr. McPherson, and Dr. Babalonis to say let's
21 summarize this, and let's have something, either a
22 work group and/or white paper, or a publication,

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1 something that comes out of this -- how can the FDA
2 really push back against this narrative, that is a
3 very dangerous and propagandic narrative, that
4 supports an agenda but doesn't really speak to the
5 health concerns of people living with debilitating
6 pain, and the practitioners, and the healthcare
7 professionals that are there who would advocate and
8 want them to live as healthy lives as they can; all
9 the different areas of expertise that are involved
10 as represented on this call. Thank you.
11 DR. STAFFA: Thank you for your comment.
12 Dr. Sandbrink, did you have a final comment
13 on our prioritization question? Go ahead.
14 DR. SANDBRINK: Yes, just actually two
15 thoughts or two comments. Friedhelm Sandbrink,
16 Veterans Health Administration, VA.
17 First of all, in regard to the role of the
18 pharmacists, we in the Veterans Health
19 Administration have used pharmacists greatly,
20 obviously recognizing expertise, but in addition,
21 using them also as providers and supporting care
22 administration and care delivery.

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1 What we notice is there are clearly these
2 differences between states. I think some kind of
3 effort to try to standardize the role of the
4 pharmacists, including where they have prescribing
5 authority and others, may really help us all to
6 make better use of these great medical providers
7 with the expertise that they have.
8 The second one that I just wanted to mention
9 is specifically in regard to buprenorphine for pain
10 management. There's really a lack of, I think,
11 understanding or really a need in regard to more
12 education, and possibly a research need, to try to
13 understand this better.
14 There's a lot of information available about
15 buprenorphine. Much of it is related to,
16 obviously, using it as medication for OUD
17 treatment. But I think specifically for pain
18 management and what is the analgesic potential of
19 that medication, and how to make best use of this,
20 especially in regard to medication conversions in
21 regard to analgesia, I think there's a lot of need.
22 Thank you.

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1 DR. STAFFA: Thank you so much.
2 Well, I want to thank everybody for a very,
3 very full discussion. I know we asked for a lot,
4 but we got a lot of great thoughts. We have a lot
5 to bring back to the ranch for some great
6 discussions and some ideas for how to continue the
7 momentum. I can promise you that we are committed
8 to follow this through and to see where this takes
9 us, so we can improve the science in this area.
10 With that, I'm going to turn it back over to
11 Dr. Chai, who will be, I think, closing our
12 meeting. Thank you.
13 Closing Comments – Grace Chai
14 DR. CHAI: Thank you, Dr. Staffa.
15 I hope I speak for many others that this was
16 really such a fantastic workshop for me. I believe
17 that we've achieved our main goal for this meeting,
18 which is collectively, for many of us -- and I hope
19 we've all learned something new -- more on the
20 science underlying the space, which we are
21 referring to as morphine milligram equivalents or
22 MME.

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1 As you can hear, it's much broader than what
2 we may have initially come in with. I stated
3 earlier, the allure of MMEs is in its simplicity,
4 but as demonstrated by all the presentations and
5 discussions that we've had, it's anything but.
6 This is hard and challenging, but as reinforced by
7 all the patient voices we've heard, as well as
8 comments to the public docket, it is critical for
9 us to keep leaning in when it is hard and together
10 push forward to advance the science in this space.
11 For the patients and public health, we need
12 to better equip all stakeholders with the tools and
13 with a better more thorough understanding of the
14 science and advance in the gaps when we don't have
15 enough information.
16 I truly hope you've enjoyed the
17 presentations as much as I have. We will be
18 posting meeting slides and recordings in a few
19 weeks, with the transcript to follow at a later
20 date, closer to August. As you can see, this was a
21 tremendous amount of discussion, so that transcript
22 will be available later.

1 We encourage attendees to please share the
2 materials to amplify what we have learned over
3 these past two days to really share in this
4 knowledge base that we've developed here. I'd also
5 like to give a huge thank you to all the
6 participants, especially the speakers, panelists,
7 and moderators for your time and efforts. We know
8 it took a lot of time to devote these two days from
9 your busy schedule and also the time and efforts
10 that it took to prepare for this meeting, so thank
11 you for that.

12 Also, as you can see from the presentations
13 themselves, we cannot do this alone. It truly
14 takes a village, a diverse group of experts and
15 stakeholders coming together with a common goal of
16 advancing the science in this space.

17 We also wholeheartedly thank all the
18 patients, public comment speakers, and the audience
19 for sticking with us over these past two days as we
20 work to drive the science forward to inform and
21 enhance the science underlying MMEs. Hearing from
22 the lives and the real-life experiences behind the

1 So thank you again for joining us in this
2 two-day virtual scientific workshop. Thank you to
3 the AV staff. I really want to highlight you.
4 This is not easy. They have been on top of their
5 game this entire time in preparation for this
6 meeting and have been so compassionate, and
7 educational, and helpful throughout this time.

8 I'd also like to express my huge
9 appreciation and thanks to the FDA staff and all
10 those others that have been meeting, frankly, for
11 years to help develop this meeting. So thank you
12 to everyone, and we look forward to talking to you
13 again soon. We will now adjourn this meeting.

14 (Whereupon, at 4:50 p.m., the workshop was
15 adjourned.)

1 numbers is critical and important in the
2 consideration and development of the science.

3 I would especially like to express my
4 sincere thanks and appreciation to those who spoke.
5 I know this. Public speaking is not easy, and it
6 is especially courageous to share about your own
7 personal life and struggles. And for those who
8 were not able to speak for various reasons, please
9 post your comments in the public docket. We will
10 be reviewing them all. All comments are valued.

11 Just to end, this is a part of something
12 much bigger than just this one meeting and it
13 cannot be done alone. Seeing and hearing all that
14 is unknown, what needs to be done, or infeasible,
15 or too hard, it may seem overwhelming, but looking
16 at the glass half full, even in this meeting alone,
17 we learned a lot. There have been new studies
18 shared, new insights, and a better understanding as
19 a whole, especially of the need, and identification
20 of the problems, and the gaps, and the need in the
21 science are actually huge steps forward in
22 advancing the science.

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