FDA Public Virtual Scientific Workshop - Day 2
Morphine Milligram Equivalents

June 8, 2021

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FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research (CDER)

Public Virtual Scientific Workshop

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

Day 2

Tuesday, June 8, 2021
9:00 a.m. to 4:50 p.m.

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Welcome and Introductions

DR. CHAI: Good morning and welcome back. Thank you for joining us virtually for day 2 of this Public Scientific Workshop on Morphine Milligram Equivalents. I would first like to remind everyone to please mute your line when you are not speaking.

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

First, I would like to start with a few housekeeping details. Meeting materials, including the agenda, the list of speakers, panelists' names and disclosures are available online and posted on the meeting website. Yesterday, we went through panelists' and participants' introductions. Today, I will refer you to the panelists' names and disclosures on the meeting materials website.

The public docket as cited in the Federal Register notice will be open through August 9, 2021 for your feedback. You are encouraged to post further comments there. The first break today will occur around 11 a.m. Lunch is scheduled for 12:30 p.m., if you could plan accordingly.

Our goal today is that this meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals are asked to mute and unmute to speak only when recognized by me or other moderators to help facilitate this virtual meeting.

During this meeting, only panel members, consisting of all invited speakers and panelists, will be able to ask clarifying questions of the presenters and participate in the panel discussions today. We have scheduled clarifying question sessions following groups of presentations. We encourage all panelists to jot down any clarifying questions you may have for presenters, and please take note of the times for the clarifying

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questions.
As a gentle reminder, I'd like to remind all the presenters and panelists that the arrows on the screen, if you could refrain from touching the arrows on the screen unless you are actively presenting, as it will change the view for the entire audience. So please refrain from touching the arrows on the screen unless you are actively presenting.
I will now try to provide a recap of day 1.
Can you hear me? Is the audio not coming out that good?
AV TECH: I think we can hear you fine.

Recap of Day 1 and Introduction of Day 2

DR. CHAI: Okay. I'll keep going.
I will now try to provide a recap of day 1. The presentations yesterday were excellent and provided us a wealth of information. Although I don't know if I can do them justice, I will now try to briefly summarize what we heard yesterday.
We started the day with opening remarks from Dr. Cavazzoni, the director for CDER here at FDA.

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She spoke of the difficulties of this past year, particularly for patients, and that stronger science is needed to better utilize MMEs to ensure appropriate dosing and to prevent overdoses. Conversion factors have great complexities and may have a role.
Next, I touched upon the different topics that will be presented by other speakers. An influence diagram was used to illustrate the complexities and how we cannot look at different components in a silo. Rather, it all starts with the science, and I described the resulting influences of science through the multiple applications and how they may ultimately impact patients. The opioid crisis is highly complex, and even with MMEs, there are many moving parts and should not be considered in isolation.
Ms. Cowan spoke next and provided great insight into how science impacts the real-life experiences of people with pain, the great need for a balanced approach to effectively manage pain, and how it is individualized. She emphasized the

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importance of patients' active role in the process and how patients need to be a part of their care and management of pain.
Ms. Woods presented on the many current applications and uses of MMEs in clinical practice, regulations, dispensing, and reimbursement, as well as in the research. It will be important to keep these different applications in mind as we discuss the science; that we need to better inform all these varied applications of MMEs.
Dr. McPherson provided an overview of the complexities of using MMEs for opioid conversion and rotation in individual patients, starting with the history of opioid conversion calculations, problems with MME calculations, a newer paradigm for calculating MMEs, as well as insight into opioid use in the hospice population.
Dr. McPherson also presented on the wide variation in results in the calculations of MMEs amongst even healthcare providers, the varying results from different online calculators, and other differences, highlighting the variability

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that can directly impact patient care.
She encouraged much more nuanced thinking about MME calculations and recommendations for treatments based on experience and training that one can get as a healthcare provider. This cannot be an automated decision. It is much too complex for that. Only one component of the decision making may need a math app, and there is much more complications, even with that, with the current tables.
Dr. Fudin built upon and added a different perspective to what Dr. McPherson discussed regarding the need for individualization due to differences in pharmacogenetics and varied responses attributed to differing pharmacokinetics and pharmacodynamics across patients.
Dr. Fudin also provided an overview of drug characteristics such as differences in binding affinity, partition coefficients, molecular weights, and ultimately how these may inform a range of equivalent equianalgesic doses.
The unique drug characteristics of methadone

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

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

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

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

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

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

Drs. Pittaway-Hay and Molinari presented next on MHRA's similar journey in the UK on the development of MME tables with the goals of improving information for opioid prescribers on the safest possible effective dose of morphine or equivalents.

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

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

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

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

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

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

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

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methadone, and tapentadol as further challenges in need for creative solutions.

As mentioned earlier, we highly value the public docket, and the public docket will be open through August 9th for your feedback. You are encouraged to post further comments, as we do review them and value your voice.

That concludes my recap of day 1. On the agenda today, we have six more presentations, and to kick off presentations for today, we will now hear more about opioid conversion information in regards to FDA drug labeling from Dr. O'Donnell. Thank you.

Presentation – Mary Therese O'Donnell

DR. O'DONNELL: Good morning, and welcome back to day 2. My name is Therese O'Donnell, and I'm a medical officer in the Division of Anesthesiology, Addiction Medicine, and Pain Medicine, and I will be discussing Opioid Conversion Information in Approved Labeling.

First, I'll give some general background about the amount and type of conversion information

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that is present in the labels relevant to the immediate-release, extended-release, and long-acting opioids. In addition, I'm going to go over the specific details of some safety labeling changes for opioid analgesics that provide consistency and standardization of language in the labels. And finally, I will go over the opioid analgesic risk evaluation and mitigation strategies, which FDA expanded in 2018 to cover all opioid analgesics.

Opioids have been used for the treatment of acute and chronic pain for the last several decades. During the course of treatment, as mentioned by multiple speakers yesterday, a subset of patients may need to be switched from one opioid or route of administration to another in a process known as opioid rotation. This may occur because the patient experiences intolerable side effects, does not achieve adequate analgesia, or for several other reasons.

The sections of the label that contain relevant information on opioid conversion

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information include dosage and administration, warnings and precautions, and the clinical studies section.

To briefly summarize, the labels reviewed contain general information and/or guidelines for conversion from one opioid to another with recommendations to underestimate the dose of the new opioid due to interpatient variability, possible incomplete cross-tolerance, and other factors relative to the individual patient and clinical setting.

In some of the extended-release labels, specific conversion tables that were used in clinical studies and submitted with the application are also included in the label. I will go over specific examples of these tables later. Finally, the sources of opioid conversion information referenced in the approved labeling include published literature, consensus guidelines, and specific clinical trial data.

I will now move on to review the immediate-release opioid labels. These labels

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include general information on conversion from one opioid to another and do not contain specific information in the form of a conversion or equianalgesic table.

This is the dosage and administration section for immediate-release opioids. This section provides recommendations for the initial dosing, dose titration, and when appropriate, dose tapering.

For the conversion from one opioid to another, most immediate-release opioid labels have general statements advising healthcare professionals to refer to published relative potency information, keeping in mind the conversion ratios are only approximate. Due to significant inter-patient variability in the potency of opioids, it is also recommended to underestimate a patient's initial 24-hour dosage rather than overestimate.

The relative bioavailability of immediate-release products compared to extended-release opioids is unknown, so conversion

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to an extended-release opioid must be accompanied by close observation for excessive sedation and respiratory depression.

Moving on to extended-release, long-acting opioids, all labeling includes general and, when available, specific information on conversion in the dosage and administration section. The reference to interpatient variability of relative potency is similar to the immediate-release product label.

There are also two statements in warnings and precautions relative to conversion that include respiratory depression and death that may occur if the dosage of a new opioid is overestimated when converting from one product to another and the avoidance of withdrawal when discontinuing opioids.

Extended-release opioids, as I mentioned, with data from clinical trials to support specific conversion factors may have those tables in Section 2 of their label. The most important point to note is that these conversion tables are generally just that. They are not MME or

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equianalgesic tables, and the labels include recommendations for dose modification based on the individual product, and I will now go over such an example.

This table was used as a guide in a clinical trial of Hysingla ER that had an open-label titration period during which subjects were converted from their prior opioid to the investigational product, Hysingla ER.

The conversion factors are specific only to the listed oral opioids and can only be applied in a unidirectional manner. They're only for use in converting patients to the product in question and are not to be used in the reverse direction, which could lead to overdose.

In addition, the labels that have these tables also include specific instructions on how to calculate the initial dose. For Hysingla ER, the first step is to use this table to convert the prior oral opioid to a total hydrocodone daily dose, and then to reduce the calculated daily hydrocodone dose by 25 percent to account for

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interpatient variability in relative potency. Then it recommends rounding down, if necessary, to get the appropriate Hysingla- tablet strength, maintaining close observation for signs of withdrawal or oversedation on the new regimen.

The percentage reduction of the calculated daily dose varies for each product. This is another example of a conversion table, but it is for pediatric patients 11 years and older. The OxyContin label states that there are no established conversion ratios for a conversion from other opioids to OxyContin, defined by clinical trial for adults. However, the label does have a table for conversion of pediatric patients, based on clinical trial experience.

Note that patients must be on and tolerating opioids for at least 5 days, and also note the qualification to adjust the conversion factor for patients receiving high-dose parenteral morphine, from 3 to 1.5.

I will now go over some of the changes that have been implemented across opioid analgesic

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products to improve informed prescribing. In 2016, FDA revised the package insert for all opioid analgesics. This affected the immediate-release products the most, as extended-release and long-acting opioids went through a comprehensive labeling change in 2013.

This included clear instructions regarding the choices of the initial dose of an opioid analgesic and dosage modifications when switching from one opioid to another or when titrating the dose. Later, the risk associated with abrupt discontinuation was also added.

In 2018, the opioid analgesic REMS was expanded to include all opioid analgesics used in the outpatient setting. I will briefly review risk evaluation and mitigation strategies.

REMS are intended for drugs with serious risks that could outweigh the benefits, and they can be required at the time of drug approval or during the postmarket period if new safety information becomes available.

REMS can be done in a variety of ways, and

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

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

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

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

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

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

All opioid labels do have information regarding risks of initiating an opioid, making dosing changes, converting from one opioid to another, and in discontinuing products abruptly. Thank you very much.

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

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

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

Thank you, Dr. Mellon.

Presentation – Daniel Mellon

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

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

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should not be construed to represent FDA policies or views.

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

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

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

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

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

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

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

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sometime between 1803 and 1805 that morphine was first extracted from opium resin by the German pharmacist Friedrich Serturner. In fact, morphine was actually the first alkaloid ever extracted from any plant.

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

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

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

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

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

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

Based purely on receptor binding studies and

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

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

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

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

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activation and G-protein coupling, the receptor results in multiple signal transduction events mediated by the alpha and beta gamma subunits of the G proteins. Intracellular signaling cascades result in multiple downstream effects, including inhibition of adenylyl cyclase, and thus decrease cyclic AMP and protein kinase A activation.

In addition, binding of opioid antagonists to opioid receptors result in reduced opening of voltage-gated calcium channels, which results in reduced neurotransmitter release from presynaptic terminals. Third, activation of opioid receptors results in stimulation of potassium currents through several different channels, which results in hyperpolarization of neurons.

Finally, data indicate that binding of opioid antagonists to opioid receptors leads to activation of protein kinase C and phospholipase C beta. Also consistent with other G-protein-coupled receptors, activation of opioid receptors can result in the receptors being phosphorylated by G-protein-coupled receptor kinases, or GRKs.

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Phosphorylation of the intracellular portion of the receptor promotes interaction with the intracellular protein beta arrestin, which functions to turn off the G-protein mediated signaling, helps target the receptor for internalization, and redirect signaling to G-protein independent pathways.

That leads us to the fact that opioid receptors can desensitize, and ultimately individuals can manifest drug tolerance. Let's define those terms.

Desensitization usually refers to the molecular changes at the level of receptor signaling that result in progressive reduction of signal transduction after receptor activation. For opioid receptors, there is a rapid desensitization that takes place in seconds to minutes. A short-term tolerance can occur in minutes to tens of minutes, and longer-term tolerance that can occur after longer exposures to agonists, such as days.

This is illustrated in the figure on the right side of this slide. The molecular mechanisms

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mediating this desensitization are complicated given the diverse-signal transduction events that occur after receptor binding. However, phosphorylation of the receptor after activation is believed to play a role.

After phosphorylation, the receptor may be internalized via endocytosis, resensitized, and recycled to the cell membrane or ultimately degraded. Homologous desensitization refers to the desensitization of the receptor following its own activation. Heterologous desensitization, or cross-desensitization, refers to desensitization of other receptors on the cell following activation. Both can occur and impact the overall activity of the cell.

The term "drug tolerance" is more general. This term refers to the loss of responsiveness to an agonist after continued exposure without specifying the cellular or molecular mechanism mediating the loss of responsiveness.

We mentioned receptor internalization. This is often referred to as receptor trafficking. What

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is important to note is that data suggest that the different opioid receptor subtypes respond to ligand binding differently.

For example, both the mu opioid receptor and the delta opioid receptor both undergo rapid agonist-mediated internalization after receptor activation. Data suggests that the mu opioid receptor recycles to the membrane after internalization. However, the delta opioid receptor appears to be degraded after internalization, and the kappa opioid receptor does not appear to internalize at all.

The response of the receptor following activation may actually differ depending upon the ligand studied. For example, etorphine and enkephalin binding to the mu opioid receptor results in rapid internalization, whereas morphine binding to the receptor does not appear to result in significant receptor internalization.

This is illustrated in the table on the right part of this slide. Both morphine and etorphine result in G-protein activation, but the

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mu opioid receptor is phosphorylated far more after etorphine binding than morphine binding.

This results in greater beta-arrestin recruitment and mu opioid receptor internalization following etorphine compared to morphine. In contrast, morphine binding to the mu opioid receptor results in greater PKC activation and mu opioid receptor desensitization than etorphine.

The take-home message, however, is that different ligands may result in different intracellular signal transduction cascade events that can result in different receptor trafficking responses, and thus different overall physiological responses.

This also serves to introduce the concept of a "biased ligand". As we noted earlier, opioid receptor signal transduction involves both activation of G-proteins and beta arrestins. Activation of both of these trigger intracellular signal transduction cascades.

Data suggest that beta arrestin not only is involved in receptor phosphorylation and

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desensitization but can also result in other intracellular signaling cascades that contribute to the net effect of the opioid following binding to the receptor. In fact, it has been reported that activation of beta arrestin in G-proteins may contribute to different physiological effects.

If true, then a specific opioid drug could result in greater activation of G-proteins compared to beta-arrestin pathways, which has been proposed to be associated with greater analgesic effects and less adverse side effects, while a different opioid drug that results in greater beta-arrestin activation than G-protein activation could result in greater adverse side effects and less analgesia.

Drugs that result in this unbalanced activation are referred to as biased ligands. The different intracellular signaling effects of various opioids may alter the ultimate physiological response, possibly contributing to differential efficacy, adverse effects, and rates of desensitization.

This is illustrated in the figure borrowed

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from Dr. Williams and colleagues' excellent review in Pharmacological Reviews. The X-axis represents the bias factor. A value above zero indicates a bias toward G-protein activation and a value below zero indicates a bias toward beta-arrestin activation.

DAMGO is an experimental peptide highly selective for the mu opioid receptor and shows a bias toward G-proteins, depicted in the red bar and number 1 in the figure. Morphine is depicted in the dark blue and the number 5 on this plot, and shows little bias.

Oxycodone, depicted as number 6 and orange bar, is similar to morphine. Norbuprenorphine, an active metabolite of buprenorphine, and alfentanil, depicted here in green and a slightly darker blue, or numbers 12 and 13, respectively, show a bias toward beta-arrestin activation.

Although it is not yet clear if these differences are clinically significant, the point is that not all opioids produce the same downstream signal transduction events.

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To add to the complexity, we cannot ignore the impact of genetics on basic pharmacology. Not only do genetics impact how drugs like opioids are metabolized, but there are data that suggests that a person's genetic makeup may well impact how they respond to opioid analgesics.

For example, there is a single nucleotide polymorphism termed RS1799971 that results in a change in a single nucleotide from adenine to guanine in a gene that codes for the mu opioid receptor called OPRM1. This single nucleotide polymorphism is present in 15 to 30 percent of Europeans, 40 to 50 percent of Asians, but only 1 to 3 percent of people of Latin or African American descent.

That single nucleotide change results in a change in the amino acid at position 40 from asparagine to aspartate. That's not necessarily inconsequential because that change removes an amino acid that can be glycosylated.

Glycosylation of that asparagine can impact mu opioid ligand binding, signal transduction, and

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

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

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

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

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

Dimerization of receptors can impact ligand binding, intracellular signaling, and receptor trafficking and desensitization. Even more challenging, hetero dimers can occur such that a mu opioid receptor could dimerize with a kappa opioid receptor. Likewise, a delta opioid receptor could dimerize with a kappa receptor, and a mu opioid receptor could dimerize with a delta opioid receptor.

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

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

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

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

Activation of the kappa receptor has also been linked to analgesia, as well as anticonvulsant effects, depression, dissociative effects, hallucinations, neuroprotection, and even stress. Drugs which act at multiple opioid receptors, sometimes referred to as mixed-opioid agonists/antagonists, may have slightly different effect profiles.

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

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

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

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

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

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

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

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

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

To compare affinity, we compare the concentration at which 50 percent of the receptors are occupied by the radioligand. In a direct binding assay, affinity is defined by the K or K_d dissociation constant. The K is the concentration $_d$ at which 50 percent of the receptors are occupied. The smaller the K, the higher the affinity of the $_d$ drug for the receptor.

In an indirect binding assay, we define affinity as the K or inhibition constant. The K $_i$ $_i$ is the concentration at which 50 percent of the radioligand is displaced from the receptor. The smaller the K, the higher the affinity. This gives $_i$ us a way to compare receptor binding affinities for various compounds like opioid analgesics.

Binding affinity measures how well a

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

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

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

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

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

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

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AMP levels like opioids do, the drug actually increases intracellular cyclic AMP levels upon receptor saturation.

This categorization of drugs is useful to help compare opioids which show diverse responses. In fact, in experimental opioid pharmacology, DAMGO is considered the full agonist, and many FDA-approved drugs do not produce the same magnitude of effect as DAMGO in various experimental conditions, indicating that this may not be an all-or-nothing phenomena, and drugs show varying degrees of full agonist activity.

Several years ago, FDA conducted studies to compare binding affinities of clinically-used opioid analgesics as a surrogate for opioid potency. The challenge at the time was to obtain data to help delineate what opioid drugs were more dangerous than others in order to have data to inform opioid drug product disposal recommendations in labeling; for example, recommendations of flushing unused drugs down the toilet rather than other means of disposal that could result in

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increased risk for diversion or inadvertent exposure to household members or pets.

As part of that process, Dr. Volpe and her team reviewed the existing published literature to see what data were already available to compare opioid receptor affinities with the focus on a mu opioid receptor because activation of the mu opioid receptor is known to result in respiratory depression.

The review of the literature concluded that there is a wide range of binding affinities reported for opioid compounds at the mu opioid receptor. This is likely due to differences in methodology; for example, the radioligands used, the compounds used to define nonspecific binding, the laboratory methods employed, the tissues evaluated, the species tested, just to name a few.

This figure depicts the range of K values reported in the literature for binding affinity measurements of ligands at the mu opioid receptor. The Y-axis lists the clinical opioid analgesic and the X-axis list the K value, or indirect binding

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constant, in nanomolar concentrations.

I must point out that this is a log scale. Morphine binding is depicted in the darker green color and range from less than 1 nanomolar to almost a thousand nanomolar. Fentanyl, in red, ranges from 0.01 nanomolar to approximately 200 nanomolar.

There are some expected trends from these data. For example, a compound like sufentanil, in burgundy at the top-left of the figure, generally shows lower K values, meaning higher affinity, than a compound like codeine, the black bar near the bottom-right of the figure. However, given the variability in these reported binding affinities, use of these data for direct comparisons was not considered ideal.

Similar ranges for binding affinities of these compounds were also reported for delta and kappa binding sites as illustrated in these two figures. Clearly, relying on the diversity of data in the published literature was not going to be ideal to compare FDA-approved opioid drugs given

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the variability in the results that reported.

Therefore, Dr. Volpe and her team attempted to eliminate as many confounding variables as possible to generate a single set of data for FDA-approved analgesics in order to obtain a uniform assessment for ranking of mu opioid receptor binding affinities. To do this, they employed an indirect receptor binding assay, as we described just a few moments ago, to determine the affinity of FDA-approved opioid analgesics.

Specifically, these binding data generated K values using radiolabeled DAMGO displacement from commercially available tissue preparations, expressing recombinant human mu opioid receptors. This approach standardizes the tissues and receptors being studied, the radioligand employed, the definition of specific binding for the assay, the laboratory methods, and even the scientists who completed the actual assays.

The result was some of the prettiest receptor binding plots I've ever seen, and I take no credit for these. The indirect binding

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displacement plots are on the left, showing displacement of tritiated DAMGO from the receptors for each compound. The K values in nanomolar are in the table on the right, ranked from highest affinity to lowest. Remember, a low K means a high affinity of the compound for the receptor. The red box depicts the K for morphine, which in this system was one 1.168 nanomolar.

Many of these affinities are consistent with what we would expect. For example, sufentanil, hydromorphone, and oxymorphone have higher affinity for the mu opioid receptor than morphine and are believed to be more potent. Likewise, codeine and tramadol have lower affinities than morphine and are known to be less potent than morphine.

As we heard yesterday from Dr. Fudin, codeine is metabolized to morphine, so we do have to take that into consideration when comparing potency. Tramadol has a very low affinity, but that actually makes sense as well because we know that tramadol itself does not really bind to opioid receptors; rather it is the M1 metabolite of

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tramadol that binds to the mu opioid receptor.

But let's look at these data a bit closer. The slide is small, granted, but fentanyl, which we know is commonly considered to be about 100 times more potent than morphine as an analgesic, has a binding affinity which is actually slightly lower than that of morphine, a slightly higher K. Likewise, oxycodone, commonly considered to be about 1 to 2 times more potent than morphine, actually has a binding affinity that is 22 times less than morphine.

Yesterday, we heard from Dr. McPherson that the difference may be, in part, due to very different oral bioavailability for oxycodone compared to morphine. Clearly, binding affinity alone does not predict potency in all cases, but understanding how a drug binds to the receptors is an important piece of information to consider when considering opioid comparisons.

Unfortunately, we don't have comparable data for uniform binding affinities for these opioid analgesics to kappa or delta opioid receptors, as

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that was not the aim of the study at the time.

Now let's explore these data a bit further by looking at other factors that may contribute to opioid potency. In this table, we present the mu opioid binding affinity data we just looked at and compared, as available, to reported rat oral LD_{50} values. LD_{50} stands for the dose that is lethal in 50 percent of the animals.

We don't generate these data anymore, as these studies require a large number of animals in order to be accurate, although comparing these values does provide a relative understanding of the lethal overdose potential of various drugs.

As we expected, fentanyl is very potent in terms of potential lethality. It has an LD_{50} of 18 milligram per kilogram in the rat. In contrast, the LD_{50} for morphine in this model was 461 mg/kg; that is, it takes about 25 times a higher dose of morphine to result in 50 percent mortality compared to fentanyl.

The potency of fentanyl, as we heard in Dr. Fudin's presentation yesterday, can in part be

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explained by its lipophilicity. Drugs that have a high lipophilicity partition into fat, and therefore can cross the blood-brain barrier quickly. We can measure lipophilicity by comparing how well a compound partitions in something that analogous to fat like octanol versus water.

In the table, I have listed the octanol-water partition coefficient. We can see that fentanyl partitions into octanol quite well compared to water, 860 compared to 1. In contrast, the octanol-water partition coefficient for morphine is 1.42 to 1, which makes it far less lipophilic. Lipophilicity clearly contributes to potency in vivo.

Now let's look at buprenorphine. We know that buprenorphine is a partial agonist at the mu opioid receptor. Receptor binding affinity is actually about 5 times higher -- 5 times smaller K value, compared to that of morphine. In other words, it takes about 5 times lower concentration of buprenorphine to occupy half the receptors compared to morphine. However, because it is a

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partial agonist and does not result in maximal activity, even when 100 percent of the receptors are occupied, the oral rat LD_{50} is estimated at greater than a thousand milligram per kilogram.

The take-home message here is that binding affinity alone, although one important way we can compare opioids, does not completely dictate potency, and many factors have to be considered when comparing opioids.

There are many experimental ways to measure potency. For example, there are in vitro assays such as the receptor binding studies we just examined or in vitro studies to measure G-protein, activation, inhibition of adenylyl cyclase, calcium influx, or cyclic AMP inhibition. Each of these assays contribute to our understanding of the cellular responses following opioid receptor-ligand binding.

There are also in vivo studies that can be used to compare opioids. For example, we can measure pain responses in animals by studies such as the tail-flick assay, or study responses to

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painful stimuli in knockout animals; for example, animals that lack specific receptors or express differential receptor variants.

However, the challenge with any of these assays is the same faced by Dr. Volpe and the FDA team. We do not have uniform data for clinically-relevant opioids in each of these endpoints.

Let's discuss more of the challenge of extrapolating animal pain responses to humans. In humans, we measure analgesia, which is defined by Merriam-Webster as "insensitivity to pain without loss of consciousness." This is commonly assessed by asking the person how much pain they feel using a variety of scales such as a visual analog scale; for example, rate your pain from 0 to 10, with 0 being no pain and 10 being the worst pain you've ever felt or unbearable pain.

We know that there is both a sensory and an emotional component to analgesia in humans. For example, opioids not only alter signaling of pain from a banged shin to the brain via the pain

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pathways, they can also impact our emotional response to that pain that we do feel. We can also measure children's perception of pain using a scale with images to help depict how they feel such as the faces scale depicted here.

We heard yesterday that assessing pain responses and analgesia in humans is not simple, but it's even harder in animals. As we know, we cannot discuss with animals how much pain they feel, and we have no idea about their emotional response to a painful stimulus. As such, we don't use the term analgesia in nonclinical research; we use the term anti-nociception. Anti-nociception, according to Merriam Webster, is "the action or process of blocking the detection of a painful or injurious stimulus by sensory neurons."

One early method used to measure anti-nociception is the tail-flick assay. In this assay, you must first acclimate a rodent to the testing process and apparatus to minimize the impact of stress on the animal. Once the tail is comfortably lined in a small groove on the surface

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of the device, you shine a radiant heat source, basically a light beam, on the tail and measure the amount of time it takes for the rodent to flick the tail away from the light.

The assay conditions are such that the heat source does not injure the tail; only makes it uncomfortable enough to result in the animal flicking it away from the heat source. If a drug produces anti-nociception, the rat will not flick the tail as fast, if at all.

Please note that the study conditions are established such that if the animal does not respond by flicking the tail away, which can occur with opioids, the heat source times out to prevent tissue injury and inflammation.

The tail-flick assay has been around since about 1941. This image from Dr. Gonzalez-Cano and colleagues' excellent review describes the evolution of the various assays that have been investigated to try to measure nociception in animals.

As you can see from the figure, more recent

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models are trying to include emotional responses to painful stimuli in the animals by including endpoints of behaviors thought to signify stress and anxiety, including burrowing behavior or nesting, and even more recent attempts to evaluate facial expressions in the animals.

The important point here is that there are many ways to assess the response to stimuli in nonclinical models, but they are models and may or may not entirely predict potency of analgesics in humans. Nonetheless, they are extremely useful for drug discovery and could be employed to generate a uniform assessment of FDA-approved opioid analgesic potency and contribute to the body of knowledge we currently have.

Unfortunately, we are not aware of a comprehensive uniform assessment of FDA-approved opioid analgesics in any of these models, and significant variability can occur between laboratories and methods used to make cross-study comparisons challenging.

To conclude, there are certainly both

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strengths and limitations of nonclinical assays. In vitro studies have utility in that they can focus in on one or a few endpoints relevant to opioid pharmacology and opioid receptor potency comparisons such as measurements of opioid receptor binding or intracellular signal transduction events. However, there is inter-laboratory variability and generally a lack of uniform assessments for all FDA-approved opioids in any single model.

In vivo nonclinical studies can also provide useful information to compare opioids, however, there are species and even strain differences, receptor density differences, and possibly differences in metabolism and transport in animals compared to humans.

Although nonclinical data are useful to inform the basic science of opioid pharmacology, there are clearly translational challenges with nonclinical studies, such as attempting to predict analgesia in humans by measuring anti-nociception in a highly controlled animal model.

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The question we all face is, is it possible to develop an ideal algorithm to account for all variables that contribute to analgesia and adverse event profiles for a given individual in order to compare opioids? Possibly, but the data clearly indicates that there are both drug and drug product factors that should be accounted for, as well as individual patient factors, as we have heard about in prior talks.

For example, drug and drug product specific factors include the selectivity of the drug for various opioid and non-opioid receptor in the pain pathways and the impact of genetics on receptor expression and receptor splice variants that can contribute to variability in responses.

The dosage form and the route of administration clearly impact efficacy and safety, the relative bioavailability of different compounds and dosage formulations, the affinity and avidity of the drug for the targeted receptors, the rate of desensitization, and even protein binding characteristics all contribute to variability for

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any given individual.

As we have heard in earlier talks, there are also individual patient factors that would also have to be accounted for, including age, sex, body mass, kidney and liver function, degree of existing tolerance, concomitant medications, and supplement use. Underlying disorders and of course genetic differences in receptors, enzymes, and transporters can all result in differential patient responses.

I will end with some final thoughts. As we all know, opioid pharmacology is incredibly old, and yet there's still a great deal unknown. Basic science and nonclinical studies can certainly contribute to the foundation of knowledge we need to help understand the variables necessary to be able to compare opioid potencies for a given individual.

However, cross-study comparisons of in vitro and in vivo nonclinical data in the published literature are extremely challenging, given the variabilities that exist and methods employed; and in theory, uniform assessments may help standardize

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values that could be considered in an algorithm. Obviously, we cannot just look at one endpoint to predict cross-opioid comparisons. We need to consider the relative contribution of the many variables that can impact outcome in order to ultimately develop an ideal algorithm.

Finally, it is worth noting that nonclinical studies can inform on specific differences between opioids in a highly controlled setting, but the results require integration into the entire body of knowledge and ultimately testing in the clinical setting, given the variabilities present in humans.

On behalf of Dr. Volpe and myself, we want to thank you for your attention today, and we hope that you are finding the workshop both informative and useful.

DR. CHAI: Thank you, Dr. Mellon and Dr. Volpe. That was fantastic. I know you're calling it basic opioid pharmacology 101, but you just broke down such complex topics in a way that was digestible for us, and just really appreciate the overview that you did. I'm sure that it's

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going to really help in our discussions, especially as we tackle questions like question number 2 in our panel discussions, so we look forward to that time later today.

Now, we'll hear from Dr. Chad Reissig, who will provide an overview of abuse liability considerations from an FDA perspective.

Thank you, Dr. Reissig.

Presentation – Chad Reissig

DR. REISSIG: Great. Thank you so much.

Today I want to talk about MME Calculations and Abuse Liability Considerations. I'll give you a quick overview of today's talk.

I'll begin by talking about what is addiction, how do we measure and define it, and then I'll move to discussion about addiction in a regulatory context. This is where I'm going to spend the majority of the time of my talk, where I'll be talking about abuse liability assessment, focusing on two main areas.

These are the preclinical methodologies that we use, more specifically, self-administration

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studies in rodents, and I will also discuss clinical abuse liability assessments, the studies that we do in humans. What we want to talk about is whether or not there is a role for abuse liability assessments in MMEs.

What is addiction? It's a complex behavioral syndrome that's defined in a number of ways. For example, the National Institute on Drug Abuse says that, "Addiction is defined as a chronic relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences."

The Substance Abuse and Mental Health Services Administration, or SAMHSA, says that, "Substance use disorders occur when the recurrent use of alcohol and/or drugs cause clinically significant impairment, including health problems, disability, and failure to meet major responsibilities at work, school, or home."

Drug abuse can be defined as the intentional non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or

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physiological effect, and repeated incidence of drug abuse may in fact lead to addiction.

So how do we measure addiction? Well, unfortunately, there are no biomarkers or laboratory-based assessments that are able to diagnose or measure addiction. I can't draw a patient's blood or scan their brain to come up with an objective indicator of addiction. And in fact, clinical diagnosis and outcome measures of addiction are usually qualitative in nature. For example, they include things like the Diagnostic and Statistical Manual of Mental Disorders, which is now in its 5th edition, DSM-V, and diagnoses in the International Classification of Diseases, or ICD.

So, for today's discussion about addiction abuse liability and MMEs, morphine milligram equivalent calculations, they do not currently take abuse liability considerations into account and, in fact, this is appropriate due to the complexity of including abuse liability as part of the composite MME calculation and also difficulties in defining

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addiction and abuse potential as a discrete phenomena.

However, we do have a variety of scientific methodologies that we utilize to both evaluate and predict the abuse potential of drugs, and FDA actually has a guidance on this. As described in our final guidance, the Assessment of Abuse Potential of Drugs, A Guidance for Industry, we use a variety of data to evaluate abuse potential, including chemistry information.

If a new drug is under review, we'll take a look at the basic structure of the drug and see if it resembles a known drug abuse. Receptor-ligand binding studies that Dr. Mellon just talked about are also used, along with functional studies like indices of the activation of second-messenger pathways.

Pharmacokinetic studies can be used in abuse liability assessments and abuse related studies in animals. These typically include things like general behavioral observations, what happens when an animal is administered a particular drug; drug

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discrimination studies; self-administration studies; and also physical dependence studies in animals.

Abuse-related studies in humans are also used, and this includes the human abuse potential study, or the HAP, which is our gold standard of abuse liability assessment, and also physical dependence studies that are able to give us an idea of withdrawal-related effects that may occur if a patient stops taking a drug.

Abuse-related adverse events from clinical studies are also used, and we can look at an AE profile across all phases of development to see if we see things like incidence of euphoria and other measures.

Information related to overdose during clinical studies has been utilized in the review of new drugs, and we can see from the case report forms what happens to patients and the circumstances surrounding these. And finally, assessment of the incidence of abuse during clinical studies; on occasion, subjects may begin

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abusing a particular test compound during the developmental stage.

Of those studies, the ones that I want to talk to you today about are assays that directly assess the reinforcing effects of drugs because these may be the most relevant to MME calculations. The two that I'd like to talk about are abuse-related studies in animals or the classic self-administration study, and also I want to take some time to talk about the human abuse potential study, the HAP study.

Starting with self-administration, this is often considered the nonclinical gold standard of abuse liability assessment. When you use this technique, a laboratory animal has the opportunity to either obtain or self-administer a drug. If the drug is self-administered, we can track how often and how much.

Here's a cartoon depicting the basic setup of a self-administration study. What you see here is a classic operant chamber, and on the right-hand side of the chamber there are two levers along with

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a cue light. That cue light is illuminated to indicate to the animal that the session is in fact active, that they can press the lever, and then response will occur.

Typically, the animals undergo a surgical procedure in which an infusion pump is surgically implanted into the back of the animal, and through this pump we can then self-administer drug when the animal presses the correct lever.

These are the data that we get from self-administration. What I'm showing you here is an unknown or new drug with suspected abuse potential, and you are looking at the type of data that would be generated if, in fact, the drug was reinforcing. What I'm showing here is the classic inverted U-shaped self-administration curve. You get this curve in self-administration studies when we examine a variety of known drugs of abuse.

I'll take a minute to orient you to the axes here. On the X-axis, we have the unit dose of drug, and on the Y-axis, we have the number of drug injections per hour, although it could be along a

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variable time schedule such as 2 hours, 4 hours, or even a 24-hour self-administration procedure.

All the way to the left, you see a placebo condition, and you see that when an animal receives saline or placebo, it typically does not self-administer very much, and likewise, as we move from left to right, low doses of a drug of abuse typically do not engender a lot of self-administration.

As we increase the dose, we see that the animal begins to self-administer drug, reaching a peak in the middle of the graph. Now something interesting happens if the dose continues to increase, and that is that the self-administration actually decreases.

Now, the reasons for this aren't entirely known, but we think it may happen for a number of reasons. One is satiation. The dose is high enough. The animal had enough. He doesn't need to self-administer very much of the drug because the dose is so high.

Sometimes a drug may produce direct

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impairment, which also can decrease the self-administration of the drug. A good example of this would be with a sedative type drug, where if the dose is high enough, an animal may self-administer it once and go to sleep for the rest of the session. And finally, at higher doses, a drug may actually become aversive, so that may also account for a decrease in self-administration as the dose decreases.

Self-administration studies in animals, they offer information about the range of doses of a drug that are reinforcing, but they are limited in determining relative reinforcement effects of drugs; for example, whether one drug has increased reinforcing effects compared to another.

One reason this is, is because of that inverted U-shaped curve that I just showed you. Oftentimes, we may not know where along that curve we lie, so we may not know whether we're on the ascending or the descending side, so it's rather hard to make direct comparisons using basic self-administration procedures.

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Because of that, generally, human abuse liability assessments are considered face valid and highly relevant indication of abuse liabilities. If human abuse potential studies and nonclinical studies do not show the presence of rewarding effects or abuse-related behaviors, then we think that widespread abuse of the drug is in fact unlikely.

How do we do these human abuse potential or HAP studies? Well, we begin in the same way that we do any clinical study, by recruitment. The study participants for these products, they typically include individuals with prior experience using similar drugs.

We think that this may increase the sensitivity of this study, and this is because experienced drug users are often better qualified to describe and evaluate subjective effects of drugs of abuse. This is the same way you may look to an experienced food critic when choosing a particular restaurant to dine at. Also, for many participants, they may find study drugs aversive.

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To find participants, recruitment usually employs standard methodologies. We're talking about media advertisements: newspaper, magazine ads, ads on Facebook and Craigslist, but we can also use techniques like snowball sampling and refer-a-friend recruiting incentives. Drug users often run in similar peer groups, so if we're able to recruit one or two, often they have a friend that may also be interested.

Once we begin recruiting subjects, participants undergo screening procedures, and this helps determine their study eligibility. It includes a medical examination. Participants in these studies, other than their drug use, they're generally healthy, and we exclude those that have significant medical conditions.

Once we've identified potential recruits, a qualification or prescreening session is usually employed, and this session involves administration of the placebo along with an intermediate dose of the positive control. We do this to ensure that participants reliably report both liking and

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positive effects from the positive control. We wouldn't want you to go to all the trouble of enrolling a subject if they didn't like the positive control comparator.

The basic procedures for the HAP studies is usually they're done under double-blind conditions, double-dummy, and they employ it within subject designs, where each subject receives all doses of the drug. During study sessions, ratings of drug liking and other effects, they're assessed repeatedly using a visual analog scale. I'll show you an example of that momentarily.

In these studies, peak ratings of liking, they're usually the primary outcome measure, although we can add psychomotor measures. So we can do things like measure the hand-eye coordination of subjects, changes in cognitive ability, and this helps us gather information on the consequences of abuse of the new or investigative drug.

We can do two things. We can see the liability of abuse; that is how likely it is a

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participant may have used a particular drug and also the consequences of that abuse. So we can get information on whether subjects will be completely sedated and whether they will experience cognitive impairment and other effects. Using these measures, the abuse liability of the test drug is assessed by comparing its effects with those of the placebo and the positive control.

Here's the visual analog scale. This appears to subjects on a computer screen, and there's a question here that says, "Do you like the drug?" The subject will take that red line and point to an area on this scale, depicting what they think; so all the way to the right, if you really like the drug effect, or they can click all the way to the left for, "No, not at all."

When we're determining liking the drug, we can ask any number of questions. Typically, we can employ upwards of 50 to 20 visual analog scales. We can ask subjects if they like the drug; if it makes them sleepy; if it makes them feel sick; if they're becoming confused, et cetera. Using these

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scales, we can capture the subjective profile of the drug.

We have to select our dose just like any other clinical study, and as you probably expect, the dose selection in these abuse liability studies is justified, though we typically include supratherapeutic doses of the test drug. Often we want to examine about 2 to 3 times the therapeutic dose of the drug, but we'll base our dose evaluation on the data that we have. In these studies, multiple doses of the new drug and the positive control, they're assessed to determine location of the dose-response curve.

So it looks like this. On the X-axis here is dose and on the Y-axis is liking, and usually we want to do at least 3 doses to generate a dose-response curve. Unlike the preclinical studies, we want to do our best to stay on the ascending portion of the curve mostly for safety reasons because we don't want to begin dosing extremely high to make subject sick or have them experience other adverse events.

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This is the cartoon image of a human abuse liability lab. You can probably tell from the CRT monitors this is a bit dated photo. But subjects will typically sit in front of a monitor, dose in the morning with a drug, and then they can fill out those visual analog scale assessments throughout the day via computer.

So what do the data look like from these studies? Here are some of the examples of typical outcome measures in a HAP study, and these data are from Stoops et al. from 2010.

What we're looking at here are visual analog scale scores from the intravenous administration of morphine. On the X-axis of both of these graphs is time - this is a time-course assessment - and on the Y-axis is the visual analog scale score.

We're looking at two outcome measures. On the left is how much do you like the drug and on the right is, do you feel any drug effect whatsoever? The placebo condition is represented by the open circle, followed by increasing doses of morphine by the square, the triangle, and

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

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

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

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

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effects occur at doses that are much higher than efficacious doses.

I will show you that on this final slide here, these are completely hypothetical data showing the standard dose-effect curve. In green, you see the therapeutic efficacy of a particular drug for any outcome measure that you want, and on the red, the red lines depict a series of hypothetical abuse-related effects.

Starting from left to right, in that first condition, we see a scenario where the abuse-related effects actually occur at doses below the maximum therapeutic efficacy. Moving to the right, one more line, we see a hypothetical drug where the abuse-related effects are shifted slightly to the right and where the therapeutic efficacy occurs prior to the emergence of abuse-related effects, and this is a more ideal situation.

But as we move to the right even further, we see similar dose-response curves where the abuse-related effects increase, but they're

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relatively further to the right of the therapeutic efficacy. So these lines to the right represent a more ideal situation, where the abuse-related effects occur at doses much higher than the therapeutic efficacy. Thank you very much.

Clarifying Questions to Speakers

DR. CHAI: Thank you, Dr. Reissig. That was a very thorough coverage of a topic that many of us are not really familiar with, so thank you for taking the time to walk us through that.

What we have now is the clarifying questions session. What we'll do is open up to the full panel to ask clarifying questions of this session's speakers. Please note we'll take a break after there are no more clarifying questions, and we are a little bit ahead of time.

(Audio feedback.)

DR. CHAI: I think there is some feedback; if everyone could mute their phones if they're not speaking.

To remind everyone how we'll conduct this clarifying session, please use the raised-hand icon

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to indicate when you have a question, and please remember to clear the icon after you've stated your question. When acknowledged, please state your name before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide, we may or may not be able to find it, but please, if you could describe the content of what you're referring to is.

Finally, it would be helpful to acknowledge the end of your question with, "Thank you," and end your follow-up question with, "That is all for my questions," so we can move on to the next panel; and as a gentle reminder, if you could please wait to be acknowledged to speak before you ask your question.

Are there any raised hands at this time? I think I see a question.

Dr. Bettinger, please unmute your phone.

DR. BETTINGER: Hey, Grace. Hopefully you can hear me ok.

DR. CHAI: Yes, I can hear you.

DR. BETTINGER: I had a question -- or two

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here, actually -- hopefully, again, more clarifying because I know we have some time for more discussion later.

First of all, great presentations so far. The first one is more directed toward Dr. Mellon and Dr. Volpe just regarding -- Dr. Mellon was really doing a great job clarifying the difficulties in assessing, it sounded, more acute forms of analgesia in human versus animal models.

But with some of the emerging knowledge we have in terms of the differences in pain pathways that emerge in the development of chronic pain, in your experience, do you feel that we have models that we can assess opioids in terms of these activities in chronic pain models as opposed to just the, I think, acute pain models, especially from an animal perspective? Thank you.

DR. CHAI: That's a great question.

Dr. Mellon or Dr. Volpe, could you take that one? Thank you.

DR. MELLON: Sure. This is Dan Mellon. That's an excellent question. Clearly, there are

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ways that one could do that in nonclinical studies to get a better understanding of the development of tolerance that can occur over time.

In the pharmaceutical world, when it comes to drug development, a lot of those studies are typically not actually done. Many of the drug companies will look at more of an acute pain model for proof of concept, knowing that they will actually be able to assess the durability of the effect and understand the potential changes that can occur with repeated application of the product in the clinical setting.

There are clearly models that could be done out there, but a vast majority of these compounds, many of which are very old, probably do lack some of those to be able to truly understand the rate of change, if you would, the rate of development of tolerance, the rate, perhaps, of development of hyperalgesia, which is always a challenge when it comes to opioids, to better understand those.

I think that's an excellent point. It is certainly something that would have to be taken

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into consideration if we were going to try to put that information into the context of the clinical setting, which is of course the vast majority of chronic pain situations that you would be working with.

That's all that I can contribute at this point in time on that particular topic. If you'd like to ask additional questions, we can certainly entertain them.

DR. CHAI: Thank you, Dr. Mellon. That was great.

Dr. Bettinger, did you have follow-up questions to that?

DR. BETTINGER: Not to that. I had a separate question, but that was a great answer. Again, I was assuming that answer, but I wanted to, again, just clarify it, especially for, of course, our audience, too.

My second question, real briefly, was for Dr. Reissig, if I'm able to; I was checking.

Again, a similar style of a question in terms of when we're looking at these

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studies -- because I've tried to do some research in writing around abuse liability studies themselves -- one thing I've noticed is that a lot of abuse studies seem to just be in either patients -- healthy subjects - or in patients with substance-use disorders.

In your opinion, is there quality evidence out there of these studies being performed in patients with either acute pain and chronic pain? Again, in your opinion, do you feel that abuse liability could be different in those patients that, again, are suffering from different types of pain? Thank you.

DR. CHAI: Thank you.

Dr. Reissig, would you like to handle that question?

DR. REISSIG: I'm muted. Okay. Thanks. I'm unmuted now.

Yes. I think that's a great question. Typically, when we design human abuse potential studies, one of the reasons we use recreational users is because we think they're the population

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most likely to abuse a drug. We also think that since they had the most experience in using recreational drugs, they're a great population to assess abuse liability in them.

I think your question about pain in patients is an empirical one. Typically, for drug development, we would not require a human abuse potential study in pain patients specifically; they're always done in recreational users. I don't know how those two populations would differ, but I suspect that, certainly, there could be differences in them, and we might run into other complications when assessing something like liking, for example.

So if you're constantly in pain, the analgesia produced on an opioid could be desirable, and someone may say, "Yes, I like that effect." It's an interesting question whether that type of liking, how or whether it differs from the type of liking that's sought after by a recreational user.

DR. CHAI: Thank you, Dr. Reissig.

Dr. Bettinger, did you have any follow-up questions?

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

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

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

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

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conversion tables in the labels were actually from the other opioid to the investigational product; it's unidirectional. They were used in clinical trials, as I mentioned, in the open-label titration phases and submitted in the application. The FDA did not generate the conversion tables.

DR. ZHANG: Okay.

DR. O'DONNELL: So they were clinical trial data, specifically.

DR. ZHANG: Okay. Thank you.

DR. CHAI: Thank you.

I see Dr. Fine next.

DR. FINE: Yes. Can you hear me alright?

DR. CHAI: Yes. Could you please state your name and let us know who your question is directed to?

DR. FINE: Right. Thank you. I just want to make sure I was able to be audible. Yes. This is Perry Fine, University of Utah. My question is for Dr. Reissig, and it's actually a follow-up from Dr. Bettinger.

Are we able to pull up Dr. Reissig's last

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slide with the modeling of analgesia versus abuse, the green and red lines?

Great. Thank you.

In the literature, and certainly in the current media and other places, there's a lot of questioning of this phenomenon that over the course of the years has been called pseudoaddiction, and there seems to be an effort to discount the phenomenon, even though it was never experimentally demonstrated.

This slides seems to sort of beg the question and, Dr. Reissig, is there any way to distinguish -- in a person who is on opioid therapy experiencing analgesia at end of dose, as blood and brain levels go down, who's starting to have a resurgence of pain, given the emotional or the affective components of pain, as well as of opioids, is there truly any way to distinguish, or a model that could distinguish, the individual's response to a resurgence of pain and the emotional consequences of that, and a desire then to leave that with taking a drug from what would be

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attributed to an abuse, or a craving, or a drug liking, independent of pain?

I hope I've articulated that adequately, but if not, we can try and dig into it. But I hope you understand what I'm trying to get at here.

DR. REISSIG: Yes. I think that's a great question. I'm not an expert on opioid withdrawal, so I think we would need to take a look at some of the opioid withdrawal scales that are often used to evaluate that, and then examine the amount of overlap that there might be with those reinforcing effects. And I suspect there may be some challenges in disentangling those two things.

DR. FINE: Thank you.

DR. CHAI: Did you have any follow-up questions, Dr. Fine.

Thank you, Dr. Reissig for the answer.

DR. FINE: No. I'm wondering if anybody else on the panel has any insight into that. I think this is a really interesting slide. I'm wondering if there's a convergence on therapeutic efficacy and hypothetical abuse-related effects

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that are actually indistinguishable; in other words, is there another line where there's an overlap in terms of the actual human experience?

We heard a lot from the public yesterday in the commentary section about perception of abuse versus adequate pain relief, and I'm wondering if Dr. Reissig has additional thoughts on how maybe to integrate this slide, or the model, or whatever it's trying to show, in terms of effective dose in a more integrated way.

DR. CHAI: Did you want to take that one, Dr. Reissig?

DR. REISSIG: Yes, sure. I can only offer my personal speculation, but I think there probably is some overlap in therapeutic efficacy and reinforcing effects. Often pain relief is accompanied by good effects or liking, so I wouldn't be surprised if there's some overlap. Thank you.

DR. CHAI: Thank you.

DR. FINE: Thank you.

DR. CHAI: Thank you, Dr. Fine, as well.

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

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

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

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

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biopsychosocial, all those impacts that impact how they're suffering.

I don't know if the drug would have an effect on any of that or play in it; so if I could see the surveys of all of these components to really understand what's going on with the individual, and then during the same testing.

So I'm just wondering if anybody's ever done that or thought about it. It just seems, to me, there are differences that you have to stand back and look at in how to design that, and hopefully somebody will do it. Thank you.

DR. CHAI: Thank you, Ms. Cowan, and thank you, Dr. Comer.

Are there any other clarifying questions at this time?

(No response.)

DR. CHAI: What we'll do now is take a quick 10-minute break. So we'll come back and reconvene at 11:05, and we'll jump right into Dr. Babalonis' presentation. So thank you, and see you in 10 minutes.

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(Whereupon, at 10:54 a.m., a recess was taken.)

DR. CHAI: Welcome back, everyone. This has been a fantastic morning so far and really looking forward to the next session.

Dr. Shanna Babalonis will be presenting next, and she will be providing highlights from an ongoing study on the relative potency of oxymorphone compared to other new opioid antagonists in humans.

Thank you, Dr. Babalonis.

Presentation – Shanna Babalonis

DR. BABALONIS: Thank you so much, and also thank you to Dr. Reissig, who provided a great context and background for this presentation.

I'll be presenting the results of two human abuse potential studies that were conducted to examine the relative potency of both oral and intravenous oxymorphone compared to other mu opioid antagonists. I have no conflicts of interest related to the present work.

Oxymorphone is a semisynthetic opioid

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antagonist which exhibits a high degree of mu opioid receptor selectivity and intrinsic activity, as we heard Dr. Mellon present earlier. Oral and parenteral formulations of oxymorphone were initially approved by the FDA in 1959 under the trade name Numorphan. However, in 1979, the manufacturer voluntarily removed the oral product, citing commercial reasons, but there were reports at the time of high rates of misuse, particularly intravenous use.

Oral oxymorphone returned to the market in 2006 under the new trade names Opana and Opana ER. Since this time, oxymorphone misuse has increased, and the extended-release product was removed from the market due to risks associated with this misuse. However, there are really little controlled data available on the abuse potential of oxymorphone.

These two studies will examine within-subject, double-blind, and placebo-controlled studies to examine the relative abuse potential and relative potency of oral oxymorphone

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and the relative abuse potential and potency of intravenous oxymorphone. I'll start with the oral study.

The published potency and conversion estimates of oral oxymorphone are based on several clinical trials with pain patients, and an example of these conversions are listed in the table here. This table indicates that oral oxymorphone is more potent than all those listed comparators, so twice as potent as oral oxycodone, hydrocodone, and methadone, and 3 times as potent as oral morphine. However, again, we have limited studies available on the abuse potential of this oral product.

One previous study examined the pharmacodynamic effects of oral oxymorphone. It was an abuse liability study to look at extended-release oxymorphone relative to extended-release oxycodone, and those doses were based on the equianalgesic estimates in conversion tables, so the doses were 2 to 1 oxycodone to oxymorphone.

In this abuse liability study, the authors concluded that oxymorphone had less abuse liability

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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high doses of both drugs increased the total time participants could leave their arm in cold water, with oxycodone perhaps just producing maybe a slightly greater analgesic effect. Similar outcomes occurred on pressure pain. Oxycodone dose-dependently increased the analgesic effects, while oxymorphone was roughly placebo-like.

This slide displays the visual analog ratings of the item, "Do you like the drug effect?" again with oxycodone on the left and oxymorphone on the right. This is data displayed across time through 6 hours post-dose.

These are the data for 10 milligrams, 20 milligrams, and 40 milligrams. Here we can see that at the highest dose tested, 40 milligrams, the effects of the drug seemed somewhat comparable. If we look at participant ratings of street value, on the left, how much would participants pay on the street for the drug they received, oxycodone, in white symbols, again appears to produce greater effects. But its highest dose, again, the effects appear somewhat similar to oxymorphone, in yellow.

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When trained observers rate opioid agonist effects, oxycodone produces greater observable effects.

Again, we conducted relative potency assessments on most outcomes, however, several outcomes were invalid due to the substantially greater effects of oxycodone. But in general, oxycodone was 2-fold more potent on pain outcomes and 1.2-fold more potent on subjective outcomes.

For things like pupil diameter, that was an invalid comparison on this model, however, we can visually assess that oxycodone was 2-fold more potent than oxymorphone. So again, these data are in contrast to the MME conversion tables, which suggest the opposite relationship, that oxymorphone is 2-fold more potent than oxycodone.

To summarize this study, oral oxymorphone is actually less potent than oxycodone on a broad array of measures, including experimental pain outcomes. And again, these findings are in conflict with the published potency ratios derived from clinical pain studies. However, one contributing factor is the low bioavailability of oral oxymorphone, which is approximately 10 percent, compared to the relatively high bioavailability of oxycodone, which is estimated between 60 and 87 percent. However, very interestingly, at higher doses, the abuse potential appeared somewhat similar to oxycodone.

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In this study, we highlight the effects of experimental pain. If one accepts the analgesic potency estimates from clinical trials as the accurate assessment, it may in turn be that these are not predictive of relative potency for other pharmacodynamic actions, including abuse potential. However, if we looked at experimentally induced pain as a valid assay for analgesia, such as this study, then oxymorphone may have greater abuse liability than oxycodone at equianalgesic doses.

In order to fully characterize the abuse liability of oxymorphone, we wanted to look at a broader range of doses in routes of administration to fully answer this question, which brings us to study 2, where we looked at the relative abuse potential and relative potency of intravenous oxymorphone.

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Again, just to highlight the background of intravenous oxymorphone, initially in the 1970s, prior to the initial removal of Numorphan from the U.S. market, there were documented cases of opioid users injecting oxymorphone, and some reported preferring oxymorphone over heroin when injected.

Since the reintroduction of the oxymorphone products onto the market in 2006 when Opana was introduced, oxymorphone has been misused via the IV route at a disproportionately high rate compared to other prescription opioids.

IV oxymorphone has been associated with significant public health harms, including an HIV outbreak in rural Indiana in which 80 percent of infected individuals reported injecting oxymorphone, and also acute kidney injury and blood vessel and blood clotting disorders, with these latter two conditions being associated more with the excipients that are embedded into extended-release oxymorphone rather than the parent compound itself.

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Due to these safety concerns, FDA requested the removal of Opana ER from the market in 2017, and the manufacturer ultimately complied. However, generic formulations of both immediate and extended-release products remain on the market, and no controlled data are available on the abuse potential of IV oxymorphone.

The primary aims of this dose-finding, double-blind, placebo-controlled, two-site study was to compare IV oxymorphone to IV morphine, oxycodone, and hydromorphone on an array of abuse potential physiological and observer-rated effects and also to calculate the relative potency of IV oxymorphone on abuse potential and safety and physiological outcomes.

This study also served as a pilot study to look at equieffective doses of oxymorphone and the comparator opioids for a study that's going on right now that we're conducting, along with Dr. Comer at Columbia University, to examine IV oxymorphone self-administration, and that study's currently in progress.

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The methods for this current study, again, were a two-site, within-subject, double-blind, placebo-controlled, 5-week, inpatient study. Nineteen experimental sessions were conducted with one IV dose administered per session. And data, again, were collected before and for 6 hours after IV dose administration, and sessions were conducted up to 5 days per week.

The participants in this study were quite a bit different. These were otherwise healthy adults with moderate to severe opioid-use disorder, with current physical dependence on short-acting opioids and current IV use. The participants in this study were 1 woman and 5 men, 1 African-American and 5 Caucasian participants, with a mean age of approximately 33 years and a BMI of approximately 22.

All were daily cigarette smokers, and the participants in this study were using intravenous heroin and fentanyl primarily as their drugs of choice, and they were using multiple times a day, nearly every day, injecting heroin and fentanyl.

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They were also using some other drugs like alcohol, other prescription opioids, cocaine, benzodiazepine, and methamphetamine.

Participants were stabilized on oral morphine of 30 milligrams per dose 4 times a day, and during each experimental session, we administered one IV dose, and these doses are expressed as milligrams per 70 kilogram because we adjusted for body weight.

We tested a wide array of oxymorphone doses, 1.8, 3.2, 5.6, 10, 18, and 32 milligrams; similar doses of hydromorphone, but we ended it at 18 milligrams as the highest dose; oxycodone, 18, 32, and 56; morphine, 18 and 32; as well as placebo. To give some background on the dose selection, we wanted to test a very wide range of oxymorphone doses, which in previous studies we conducted included up to 18 milligrams of hydromorphone and 50 milligrams of oxycodone and morphine, so we knew that we could safely go to roughly those doses.

We also wanted to be sure to include the

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estimate for IV morphine, and the MME tables suggested that IV oxymorphone was 10 times as potent as IV morphine with a 1 to 10 comparison. So we included relatively low doses of 1.8, 3.2, 5.6 to compare to a 10-fold higher dose range of morphine.

Initially, we had included high doses of oxymorphone and morphine, 56 milligrams, but those were withheld on several occasions due to safety concerns, so those data are not presented here.

Doses of each drug were randomized in ascending order for safety but were otherwise randomized. Again, our primary outcomes here were safety and physiological outcomes across the wide range of physiological measures and subjective measures of drug effect, including VAS ratings of drug liking and street value. Again, we used a relative potency analysis using the Finney parallel lines bioassay.

This graph will display end-tidal CO2 with, again, higher concentrations of end-tidal carbon dioxide as a measure of respiratory depression, so

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higher concentrations indicating greater respiratory depression and greater risks. Again, these data are presented as a function of dose on the X-axis, so these are peak effects.

On this graph and all slides that follow, doses of the drugs will display as a line function with filled symbols indicating a significant difference from placebo. The first data point here in the circle is placebo and the triangles are morphine. Oxycodone and morphine are producing relatively minimal effects on respiratory depression. Hydromorphone dose-dependently increases concentrations of end-tidal CO2, with an 18-milligram dose being significantly different from placebo. Similar effects were found with oxymorphone, with the two highest doses producing significant effects relative to placebo.

This graph will display minimum pupil diameter with smaller values, indicating greater opioid effects. Here morphine produced modest decreases; oxycodone decreased pupil diameter with the highest two doses producing a significant

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effect; dose-related decreases from hydromorphone; and oxymorphone producing even greater effects here.

This slide presents data from the visual analog question, "Do you like the drug effect you're feeling right now?" This question was presented on a bipolar VAS scale with zero being a strong dislike, 50 being neutral, and 100 being a strong drug liking effect, so this is the only graph that will start at 50 for that reason.

Morphine did not produce any significant effects; all doses of oxycodone, pretty significant effects; hydromorphone, all doses were significant except for the lowest dose; and oxymorphone produced effects even greater than those of hydromorphone.

This slide presents VAS ratings of the question, "Do you feel high?" These data are presented on a traditional unipolar VAS scale, zero being not at all and 100 being extremely. Again, morphine produced a rather minimal effect; all the oxycodone doses produced significant ratings;

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hydromorphone produced increases in ratings particularly at the two highest doses; and every dose tested of oxymorphone produced significant ratings of feeling high.

This is the last data slide here. This figure presents participant peak ratings of street value of each of the drug doses, meaning how much would the participants pay on the street for these drug doses.

Again, morphine produced relatively low ratings, as did oxycodone; and hydromorphone produced a significant effect at the highest dose tested; whereas oxymorphone, again, produced the greatest ratings with the four highest doses being significantly different from placebo and participants reporting an approximate value of 15 to $20 dollars for each of these doses.

We also conducted relative potency analyses. Because we only tested a limited number of morphine doses, we can only compare oxymorphone and hydromorphone, and we examined equal doses of those drugs. We assessed oxymorphone and oxycodone at a

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10-fold difference dose range for these bioassays.

This is a relative potency of oxymorphone versus hydromorphone. Outcomes with dashes were not valid. Again, that couldn't be compared with this assay due to potency differences. In this table here, on abuse liability outcomes, we see the milligrams of IV oxymorphone that are roughly equivalent to 1 milligram of hydromorphone.

For abuse liability outcomes, 0.36 to 0.41 milligrams of oxymorphone was equivalent to 1 milligram of hydromorphone, and on respiratory depression outcomes, 0.82 milligrams of oxymorphone was equivalent to 1 milligram of hydromorphone. For respiratory depression, oxymorphone was 1.2-fold more potent, and for abuse liability, oxymorphone was 2.3 to 2.8-fold more potent than hydromorphone.

In oxymorphone versus oxycodone potency analyses -- again, this is milligrams of IV oxymorphone equivalent to 1 milligram of IV oxycodone on abuse liability outcomes -- 0.7 to 0.8 milligrams of oxymorphone produced effects

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equivalent to 1 milligram of oxycodone, which results in oxymorphone 12.5 to 14-fold more potent than oxycodone.

To summarize the study, all of the drugs tested produced prototypical dose-related opioid effects such as miosis and increased end-tidal carbon dioxide. The abuse potential of IV oxymorphone far exceeded all the comparator opioids, with even a moderate dose producing peak effects that were greater than or equal to all other comparator doses. We even saw significant abuse-related effects of oxymorphone at comparatively low doses, so the 1.8 to 5.6-milligram dose range.

These data align with the surveillance reports, indicating that after adjusting for prescription rates and availability, oxymorphone had been injected at the highest rates relative to other prescription opioids, with some estimates indicating that that's 7 times higher rates of injection of oxymorphone compared to other prescription opioids.

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To conclude, these high rates of injection are likely due, again, to the low oral bioavailability of oxymorphone, which we demonstrated in the first study, which may increase misuse by other routes with greater bioavailability such as intravenous use. There's easy manipulation of the oral oxymorphone product to access high doses. Oxymorphone is marketed in pills up to 40 milligrams, reinforcing the facts in abuse liability at doses as low as 1.8 milligrams.

These results could also be due to the pharmacological action of oxymorphone, including a high degree of binding affinity and intrinsic activity, rapid transport across the blood-brain barrier, and a relative high potency, particularly on abuse outcomes. So overall, oxymorphone may pose a disproportionately high degree of risk and public health harms relative to other full-agonist IV prescription opioids.

In conclusion, as we have heard across presentations, both yesterday and today, it is clear that several pharmacological and non-pharmacological factors can influence relative potency, and MME conversion tables likely don't speak to or predict the safety profiles or the abuse potential of opioids.

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I would like to conclude by acknowledging. the research teams at the University of Kentucky and Columbia, and the funding sources. Thank you.

DR. CHAI: Thank you, Dr. Babalonis. That was amazing. Thank you for the preliminary results from these ongoing studies. I think I speak for everyone that we're looking forward to seeing the final study results.

Next, we have Dr. Comer, who was also co-lead on this research, who will provide additional insights into the pharmacological and non-pharmacological factors related to opioid potency.

Thank you, Dr. Comer.

Presentation – Sandra Comer

DR. COMER: Good morning, everyone. I'd like to thank the FDA for inviting me to give this presentation and Shanna for presenting the results

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of our study.

Shanna presented data showing potency relationships for different opioids and different non-analgesic effects. I'd like to take a step back and provide a broader view to talk about both pharmacological and non-pharmacological variables that may impact on calculations of relative potency. I'll be summarizing data from preclinical studies focused on analgesic effects.

Of course, the pharmacology of the drug is a really important characteristic. One aspect of pharmacology that I'd like to focus on throughout my talk is efficacy. Efficacy is a property of the drug, but it can be expressed in different ways, depending on the experimental parameters that are used.

I was trained as a behavioral pharmacologist, and we spent a lot of time thinking about, and talking about, and running experiments to try to get a handle on this particular effect.

What I'm showing here are data from a study that was collected in rats, and just to orient you

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to the slide and most of the subsequent slides, I'll be showing you dose-effect curves, so doses along the X-axis, and in this particular figure it's percent maximum possible effect on the Y-axis.

In this study, they assessed analgesic responses -- or anti-nociceptive responses; sorry -- in these rats, where the water was maintained at 50 degrees centigrade, and they just measured the latency for the animal to flick its tail out of the water.

You can see that both methadone in the circles and morphine in the triangles produced a full analgesic response, but buprenorphine and nalbuphine did not. All of these four substances are approved for treating pain. Buprenorphine, as a partial agonist, it produces I guess about a 30 percent maximal under these experimental conditions, and nalbuphine didn't really produce much effect at all. NAQ is another partial agonist that has been used experimentally.

The red line, the horizontal line that I've drawn across this figure, shows the ED50 value, so

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it's the effective dose at the 50 percent level. In preclinical studies, this is typically the level of effect that you use to calculate relative potency of drugs. But what happens with something like buprenorphine, it doesn't produce a 50 percent response. So the question is, do you lower that red line to something like 30 percent? And if you do, then the relative potency, the general relationship still holds, but the actual doses that you come up with will be different. So that's one issue that we need to grapple with.

Another factor that we have to pay attention to is the intensity of the pain. The analgesic efficacy can differ depending on the intensity or the type, as well, of pain med that is produced or being assessed.

I'm showing you here data from a study that was conducted in rats where they used radiant heat applied to the hind paw. In the left panel are effectors for meperidine, the middle is for morphine, and in the right is buprenorphine. These drugs were all given subcutaneously, and they used

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two different pain intensities. In the closed symbols, it's low-intensity pain and in the open symbols, its high-intensity pain.

For all of these drugs, there's either a rightward or a downward shift in the dose-response curves. So when the pain intensity is high, it takes larger doses to produce an analgesic response, so that kind of makes sense. With buprenorphine, whereas with the low-intensity stimulus, it produces a full analgesic response, under the high-intensity stimulus, it can no longer produce a full analgesic response.

The intensity of the pain is important, but the route of administration is also important. We heard about this yesterday with Dr. McPherson, that trying to calculate relative potency based on route of administration can be really complicated, and this figure illustrates that.

On the top panel, I'm showing you the data again that I just showed you, the subcutaneous route of administration. But when you look at those same drugs given intrathecally, you see a

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very different pattern of effect. When given intrathecally, meperidine produces analgesic responses that are pretty much the same regardless of the intensity of the pain. With morphine, there's maybe a slight rightward shift in the dose-response curve. But with buprenorphine, there's basically no analgesic response when it was given intrathecally under the high-intensity pain condition.

So this is another very complicating factor. In this study, they also looked at even higher efficacy opioids than the ones I'm showing you here. They compared the effects of hydromorphone, fentanyl, and sufentanil, and this relationship differs for those drugs as well.

Another thing that we've kind of touched on in the last couple of days is the level of physical dependence and how that impacts on calculations of relative potency. What I'm showing you here are data from a study that was collected in rats using a radiant heat tail-flick assay.

What they did was, in the top panel, they're

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

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

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

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

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

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

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

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

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

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

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forward to a really robust discussion today.

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

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

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

Presentation – Nabarun Dasgupta

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

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

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had a hard time convincing colleagues that subtle choices have big consequences since then. So we initiated this research to set things straight.

Today, I'm going to show you something that once you see it, you can never unsee it, something that will fundamentally change how you view daily MME and a 90-MME per day threshold. This study was funded by FDA and the Department of Justice, but the views are not necessarily endorsed by these agencies. Maybe they will be someday.

The materials in this analysis are also freely available, and we're giving universal permission for reuse. The details are all available at go.unc.edu/mme, and the paper has been accepted at Clinical Journal of Pain and should be available in a couple weeks.

We've also translated all the SAS code, Python code, and data [indiscernible] code to help others using these metrics. We'll get bar code up there soon. And as I speak, the slides should appear on Twitter. We're doing a little bit of experiment with links to papers and additional

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resources. We'll see how that goes.

So far in this workshop, we have heard a lot about how conversion factors are imperfect. The purpose of this presentation is to show you something new. We reveal that there are more even more fundamental and more influential issues with daily MME calculation than conversion factors and pharmacology alone.

The problem is that there are actually four different ways to calculate MME per day, but these differences have been entirely overlooked. The solution we offer is a clear understanding of how to calculate daily MME and how to choose between the different definitions.

The daily MME has been enshrined into law in 14 states, which make the assumption that daily MME is a standardized clinical metric. The MME is not a standardized clinical metric. None of the laws define how to calculate MME per day because they assume that it is a clinically standardized metric.

To start with, let's imagine that we give four analysts the same data and ask them to

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identify which are the, quote/unquote, "high-dose opioid analgesic" patients; same time period; same location; same patient; same prescription; same identical data set. We can even specify which conversion factors to use and tell them to use 90 MME per day to define high dose. And then we can tell them to only use daily MME definitions that were vetted by and cited in the CDC guideline. It sounds like a pretty boring experiment, right?

Well, this is how it plays out. Each of the four analysts identify a different set of patients who are high dose. They agree at the extreme top and bottom of the range, but in the space where most long-term patients fall, there was simply no consensus. What happened? How is there any room for variability here? They were using the same conversion factors. So something beyond pharmacology is happening here.

To get to the root of the problem, let's give the same four analysts a simple scenario. Here is a patient with two prescriptions. Both prescriptions are dispensed on the first day of a

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30-day month. We modified this example that appears in the CDC CME training module by adding one more script. If you're following along at home, you may want to screencap this slide. I promise this won't be more complicated than basic arithmetic.

The first script is 30-mg ER oxycodone twice a day for around-the-clock pain for 30 days, so we're looking at 60 tablets which have 2700 mg MME, assuming a 1.5 conversion factor. For the second script, it's one 5-mg oxycodone twice a day as needed for breakthrough pain for the first 7 days, 105 mgs, for a total of 2805 MME between the scripts. So you might want to jot down 2805 because you'll see that number again in a moment.

Four analysts would actually disagree on how much daily MME this patient is getting. Their calculations will range from 35 to 105 MME. Half are saying that this is a high-dose patient, the other half are saying they're not. This same thing could happen across doctors within the same clinical practice if their definitions aren't

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standardized or between a prescriber and an insurance company,

So far in this workshop, we've concentrated on the MME part of MME per day; the numerator is what we've concentrated on. What we haven't considered is the denominator, a day. To borrow a line from the musical, Rent, how do we measure a day in the life of a patient? I'll spare you for not singing the chorus, but you get the picture.

Next, I'll show you how these four measures were derived. We took a careful look at all of the studies cited in the CDC guideline to justify the 90 MME threshold. Of these, we found 18 that used daily MME. We combed over the methods and appendices and reverse-engineered the underlying equations, which none of the papers explicitly included. Look, my own paper is on here, and I am just as guilty as everyone else, and I apologize. So this is something I'm doing here today to rectify some of my own past mistakes.

In the accepted paper accompanying this presentation, we reproduced the verbatim extracts

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from each of these 18 papers, some of which I'll show you in just a moment. I know it's a little hard to believe, but the 18 studies used to establish the threshold silently used four different definitions. In some cases, the same authors used different definitions between studies without any comment. So this possibly can't be a big deal, right? Well, let's find out.

To atone for the lack of detail in my own published studies, I worked with Alan Kinlaw to reverse-engineer these equations. At its heart, the four definitions are measuring different things. What we are building to here is that 90 MME is not a standardized clinical metric. We face this challenge in other parts of medicine like with prostate-specific antigen tests, but we haven't even noticed that it's happening in pain medicine.

Next, I'm going to show you some equations, but if you don't speak scientific Greek, that's ok; just focus on the numbers. This slide is here for completeness. We've heard lots of brilliant

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discussion about the pharmacology, but that's not something that most patients, and even most doctors, feel comfortable challenging. In contrast, what I'm about to show you is nothing more than basic arithmetic. You can do this at home. I think Dr. McPherson said it best yesterday when she said, "Call a third grader."

Ready? We're going to briskly walk through and see how these equations apply to that two-prescription scenario you saw earlier.

The first definition we call total days' supply. In this definition, the numerator is 2805 that you saw earlier, the denominator is 37 days, adding up the days' supply for the two prescriptions, 30 and 7. Dividing these numbers, we get 75.8 daily MME.

This is the most common definition used in the literature, and this paper by Von Korff is the one that's by far the most commonly cited for definitions. Dr. Zhang yesterday pointed out that this was also cited in the printed CDC guideline, conferring with it de facto credibility, and this

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is the metric that often shows up in clinical data dashboards, including PDMPs.

Two things to note: first, the days' supply can exceed calendar days; that's weird; second, this definition is perverse. By adding a second script for breakthrough, you actually get a lower daily MME. On a clinical basis, this measure doesn't make a lot of sense at all, but on a population level, I see this citation and measure use all the time, in part, because it's so easy to calculate on a large scale.

The next definition is similar but takes into account overlapping days, so the denominator is 30 calendar days. Dividing, we get 93.5 daily MME. Just with this subtle change in denominator, we end up on the other side of the 90 MME threshold. This probably makes sense to most clinicians, but it was only used in 2 out of 18 studies cited in the CDC guideline. This is also the method that the HHS Office of the Inspector General recommends, and they provide a handy set of tools to calculate it in SAS, R, and

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SQL.

The third definition uses a fixed number of days for the denominator. Clinicians may be baffled, but this is actually the method that's used in a lot of papers in the CDC guideline and the single most cited paper on the risk of dose and overdose mortality, which is this paper by Kate Dunn. This definition has also been used in CDC published studies.

Going back to 2805 for the numerator, when we put 90 days in the denominator, we get 31.2 daily MME. This method gets used a lot in research, but it's unclear if those findings would have clinical relevance. In the studies cited in the guideline, 90 days was most common, but some studies use longer periods of time, up to 365 days, further shrinking the daily MME. And inpatient Medicare studies often use 13 days because that's the reimbursement cliff. We went with 90 because that is the most common.

Finally, the fourth definition, D4, is something we call maximum daily dose. This is the

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definition used in the mobile app for clinicians that accompany the CDC guideline. They call this the total daily dose in their publication, but we think maximum is a better word because it reflects the equation better.

This definition ignores days' supply and dates for the prescriptions. It assumes the maximum dose on one day, ignoring intentional self-harm. Using this definition, 90 MME plus 15 gives us 105. Not surprisingly, as you'll see, max daily dose returns the highest measurement.

This definition is actually a bit tricky to implement with staggered start overlapping scripts, but we have shared our code to help. It's worth noting that this definition is different from the one suggested by HHS Office of the Inspector General, so here we have two federal agencies saying different things on how to calculate this very essential metric.

One of the analysts on our team, Yanning, works with software engineers who process PDMP data and other large data sets. She's been frustrated

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that most software vendors won't even give you enough detail to know how MME per day was calculated, let alone explain it in terms for clinical decision making.

This is a real-world problem, guys, a practical problem that impacts clinical decision, data, and tools, and really calls into question the evidence base that underlies some of our fundamental understanding.

So we established that there are four ways to calculate daily MME. But, hey, is this all just academic? Fair question. So let me show you.

We did a controlled experiment. Imagine we have two places, and we observed that one place has a higher opioid prescribing rate than the other, 8.7 versus 7.9 per hundred adults. This is exactly the setup used in a lot of policy and intervention evaluations in epidemiology research. For our purposes, the cause of the difference is less important. Let's just agree that a difference exists and that we want to measure it.

Given the mild imbalance of rates on this

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slide, we may want to know a little bit more, like if there is a difference in the proportion of high-dose patients between these two places, so we did a study comparing two locations like we would in a policy intervention analysis.

We conceptualized this as if these were four different papers using the same exact data set, evaluating the same exact intervention or policy. The key thing to remember here is that the only source of variation -- the only source of variation -- comes from the four definitions.

Here are the methods. We used outpatient dispensing data from PDMPs in California and Florida. We chose a short 3-month period to avoid secular time trends. We defined high dose as greater than 90 MME, and we looked at solid oral and transdermal opioids -- opioid analgesics. Actually, it should have been mentioned on the slide; my apologies.

We used a CDC conversion table as equianalgesic potency. Equations allow you to substitute other potency factors, but we held them

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constant here because we're focused on the denominator.

For statistical analysis, we did three main things. First, we compared the percent of high-dose patients between Florida and California, varying only the definition of daily MME. Second, we quantified the milligram difference in average opioid dose per day, varying only the definition of daily MME.

Third, we conducted a meta-analysis seeing if four different studies using the same data set and the same conversion factors would have statistically agreed with each other. This method is used a lot in observational studies and clinical trials to evaluate if a set of studies are even comparable, if they measure the same thing. This was a method that we applied, that we borrowed from colleagues at FDA who presented something similar at an ADCOM last year. Thanks guys.

For sample size, we have about 9.5 million prescriptions representing about 4 million patients. The numbers you saw earlier were real.

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Here's the 3-month dispensing rates for California and Florida in the third quarter of 2018. We chose these places because these are two of the three most populous states in the country, and for good measure, I'll show you preliminary data from Texas as well.

Here are the California results first; same data, same conversion factors, but definitions D1 and D4, which are both used in clinical practice, show a 3-fold difference in who was perceived to be high dose.

Adding in the Florida results, we see a similar story, with D4 really identifying a lot more high-dose patients than the other three definitions. Remember, the clinicians who might be skeptical about the fixed 90-day denominator, definition 3, well, guess what? D1 and D3 are actually pretty similar.

It's worth pointing out that the definitions perform differently in each state. While D3 returned the fewest high-dose patients in California, it was D1 that was the lowest in

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Florida.

We also have preliminary data from the Texas PDMP for the first quarter of 2020 at the outset of the pandemic. You can see a similar pattern across the four definitions, but the overall proportions are lower. This could be due to time trends, but also that Texas tends to prefer IR hydrocodone way more than other places. But the takeaway here is across the three largest states in the country, these definitions disagree whether hundreds of thousands of patients are high dose or not.

Taking the same data, if we were doing a policy or intervention analysis comparing the two places, the four studies on the same data set wouldn't even come close to agreeing. Was there 39 percent more high-dose patients in Florida or was it 84 percent?

Those are big, big differences in terms of policy interpretation. In fact, the heterogeneity from definition alone is so high that we wouldn't be able to combine these into summary measures in a meta-analysis. This really calls into question a

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lot of what's published in the scientific literature, in epidemiology studies, at least.

Instead of percents, we may want to know how much higher doses were given in one place versus another. The four definitions don't even agree if the average ER-only pain patient is getting a high dose. We're going to look at those data a little bit more carefully here.

We are still comparing milligram differences between Florida and California. The vertical axis is average MME per day. Each blue bar is a different definition. The way to read this chart is that the bottom of the bar is California and the top is Florida; Florida is always higher. The height of the bar is how different the states are in terms of average milligrams of MME. Using maximum daily dose D4, you get a really big difference, but these numbers are really all over the place.

Alright. Ready? It gets worse. The means were highly right-skewed, meaning ultra high-dose outliers were driving averages to be unnaturally

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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First, if overlapping scripts decrease over time, choosing definition 1, total days' supply, will attenuate intervention effects compared to definition 2 differentially at earlier time points. Second, if ER and IR dispensing don't decline at the same rate over time, so non-parallel linearity, this same thing will happen.

Both of these prescribing trends happened in the U.S. over the past decade, so the choice of definitions has some special context in this country. We're doing some simulation studies to quantify this, but in preliminary work, the differential effect could be as high as 33 percent of the intervention effect. So the point here is that subtle choices in measurement have major consequences on interpretation of interrupted time series analyses.

We also explored what happens at the threshold boundary, comparing 90.0 as a threshold to 90.9. Where precisely do you draw that line for high dose? Published studies often don't make that very clear in the words that they use. If you

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shift the high-dose threshold from 90.9 down to 90.0, you increase the number of high-dose patients by 15 percent. That means there are a lot of patients who are being held at this artificial threshold despite the definitions not being clinically standardized.

June, an analyst on our team, thought this was unexpectedly huge, and I totally agree. He points out that these little changes in studies can lead to misclassification. So we quantified the extent of misclassification.

Think of this like a doctor and an insurance company setting the threshold on either side of that very tiny boundary, 90.0 or 90.9, something we'll think of as a rounding error. Using definition 1, the insurance company and the physician would disagree for one out of every 56 patients whether the beneficiary was getting a high dose or not. With definition 4, every 1 in 30, it's worth noting that definition 3 is the most robust to this kind of discrepancy, so for certain kinds of epi studies, it might have some relevance.

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To cover some of the limitations, we've assumed that all medications are taken as directed and we have combined cancer and non-cancer pain looking across the board for opioids. There are plenty of other pharmacological issues that we've talked about already, but because we're not combining this with an outcome measure, we're just kind of doing it as a simulation study, some of these issues are a little bit less relevant.

So which definition should we use? Toska from our team had a succinct reply. There's no one-size-fits-all approach, but at the least we need to be showing our work. As a side note, we're doubly proud of Toska for this past week being enrolled in the first class of the U.S. Public Health Service's new reservist program, so congrats, Toska.

We've heard lots of reasons for clinical caution using MME, so let me address this in terms of epidemiology and policy intervention evaluation. I don't think D1 should be used, period. D2 is the version I used.

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D3 is a more robust misclassification, so if you have messy data, this may be attractive. It also might be really good for long-term studies where there could be gaps between script refills and things like that.

D4 could be useful for very short-term toxicity studies in opioid-naïve patients where you don't have a risk of suicide, but definitely not for long-term situations. Its inaccuracy actually grows with time, and you can intuit that from staring at the equation long enough.

But candidly, right now if a paper doesn't sufficiently define how they calculate daily MME, I don't read the results. I just can't make sense of it after having done this analysis because these metrics are so fundamentally different.

We're also building a research tool to help select metrics. Here's a screencap of the prototype. If you want to be a beta tester, please drop me an email, which you'll see on the last slide. We're going to try to help some decision making from the research, policy, and intervention

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evaluation side.
In conclusion, let's turn to the folks with lived experience, to the patients and clinicians who actually think these disease definition choices matter. Here's how this plays out in practice with payers.
Arkansas Medicaid required beneficiaries with greater than 250 MME per day to be tapered to 90 mgs during an 18-month period; yet, we saw how D4 is not ideal for patients already on opioid therapy. But using the CDC mobile app, this could easily be the definition applied here clinically, while another prescriber may choose on-therapy days, say definition 2. The bottom line here is that 90 MME cannot be considered a hard threshold because it is not a standardized clinical metric.
Dr. Chidgey, who's one of the panelists here today and an author on the study had this to say. "While payers insist they're not dictating care because the patient can still pay out of pocket for the medication" -- I have many who do -- "for most patients, this is not financially feasible." She

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also emphasizes that proper pain management truly typifies the art of medicine, which we've heard from other speakers over the last 24 hours.
We also asked a pain patient representative on our team to weigh in on the analysis you just saw. Liz Joniak Grant, who often is on FDA advisory committees, as well, as the patient representative, says, "Far too often, we are victims of the good intentions of those wanting to do something about the opioid overdose epidemic, but the something that is done oversimplifies the problem and pushes cookbook medicine upon those of us with complicated medical situations. So we wait, and we suffer, and we hope it will get sorted so we can get the care we need."
And finally, Chris Delcher, one of our other authors, points out that this work is an example of how we can put PDMP data to work positively for patient care. We acknowledge that a lot of patient experiences with PDMPs might have been negative in the past, but in this case, we worked closely with the state PDMPs for this analysis, and had the

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opportunity -- [inaudible – audio gap] -- to educate them on the impact of these important consequences.
Alright. So here's my key message; little choices have big consequences. What we have seen here today, and reinforced by all the presentations, is proof that daily MME is not a standardized clinical metric. For the first time in public, we reveal that simple arithmetic might have a stronger impact on MME-per-day calculation than pharmacology alone.
Why has such a measurement failure not been detected sooner? Here's my take. Computational ease and evocative lure of molecular fundamentals collide in an optimal level of cognitive complexity to engender MMEs with an unsubstantiated aura of immutability. They're not immutable.
If you are a researcher, please, please, please state your definition. Feel free to reuse our equations, or slides, or code. In this way, we can be allied with patients to reduce the most harm with the best information. Thanks to FDA,

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Dr. Chai, and the rest of the team for organizing, and thanks to everybody for sticking around.
Clarifying Questions to Speakers
DR. CHAI: Thank you, Dr. Dasgupta. I think we can all agree that that was a very enlightening presentation and data-driven analyses to really highlight and show some of the complexities just in what you're referring to as the denominator, but very critical to consider in all the science that we are talking about today. So thank you, Dr. Dasgupta, and I appreciate your synopsis at the end. Thank you.
So what we'll do now is open the floor to our panel of invited speakers and panelists for clarifying questions for this session's speakers. Please note, we will break for lunch at 12:30, and if there are additional clarifying questions for our speakers, please jot them down. We will try to take additional clarifying questions after lunch, if we can.
As a reminder, please use the raised-hand icon to indicate when you have a question, and

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please remember to state your name before you speak after I acknowledge you so that we can have an organized session. And please direct your question to a specific presenter, if you can. Please also remember to clear your icon once you have stated your question.

If you have a specific slide to be displayed, we will try our best to get you to that slide, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you or, "That is all for my questions," so that we may move on to the next presenter.

My apologies again, but we will only be taking questions from the invited panel of speakers and panelists. We are unable to take questions from the audience.

(Pause.)

DR. CHAI: We may have lost some speakers. Dr. Parkinson, could you please state your name and your question, as well? Thank you.

DR. PARKINSON: Hello. This is Nicola Parkinson from the MHRA. It's just a very quick

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question for Dr. Babalonis.

DR. CHAI: What did --

DR. PARKINSON: Sorry?

DR. CHAI: Dr. Babalonis, you said?

DR. PARKINSON: Yes, that's correct.

You were talking about the oral availability and the IV availability, and the effect of abuse and the potency between morphine -- sorry, the oxycodone and the oxymorphone coding and about bioavailability.

But those studies are actually in a very small number of patients, especially with regards to the oral study. I mean, are those results really specific to that particular patient population? Do you think it's going to be the same for a wider population? Thank you.

DR. BABALONIS: Sure. That's a really interesting and important question. The data from the oral study and IV study show pretty tight results across participants. I will acknowledge that it was a quite small sample size; it wasn't a population study. So we would need to collect more

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population-level data to be able to really interpret the bioavailability.

But I think the key outcome that we were trying to show for that study is that whenever you look at abuse potential measures, they are not the same as, say, analgesic measures or physiological measures, such as respiratory depression and pupil diameter. So it's possible that those results would translate to a wider population, but we would have to do those studies to really determine that.

But the data within those groups was within-subject, so all participants received placebo in every dose of all the conditions, and the data pretty tightly adhered to each other, so there wasn't a lot of variability between the subjects. Thank you.

DR. PARKINSON: Yes. Thank you very much. I think your data was actually quite clear, the data which you had. It just goes to show, really, that the MME calculation and the potency calculations are really very difficult, especially as to how it's actually being administered between

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patients. So thank you very much.

DR. BABALONIS: Thank you. I appreciate your comment.

DR. CHAI: Thank you, Dr. Parkinson and Dr. Babalonis.

Are there other clarifying questions for this session?

I understand there's been a lot of material presented. What we can also do is try to address other clarifying questions that you may have regarding other presentations that have taken place over the last two days. I understand that a few of our presenters aren't able to join us today, but representatives are available to address any of the presentations, or we can try to address any of the presentations.

(No response.)

DR. CHAI: I think there's too much to digest, and maybe many of us are also hungry.

So what we can do now is break for lunch. Please, if you do have questions, jot them down. What we'll do is come back at 1:20, so please plan

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on coming back at 1:20 to begin our second half of day 2 for the panel discussions.

At this time, I'd like to welcome Dr. Judy Staffa and Dr. Jennifer Nadel, who will be moderating this afternoon session. So they will be taking over at 1:20. See you back then. Thank you.

(Whereupon, at 12:21 p.m., a lunch recess was taken.)

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

(1:22 p.m.)

DR. CHAI: Welcome back, and I hope you had a nice lunch. We've had a really great group of presentations over the last two days, and I'm just very excited to introduce our next session, as well as our moderators.

I'd like to welcome Dr. Judy Staffa and Dr. Jennifer Nadel, who will be moderating our panel discussion question session. Thank you.

Panel Discussion

DR. STAFFA: Hi. Good afternoon. I'm Judy Staffa. I'm in the Office of Surveillance and Epidemiology, and I'm happy to be helping out with this meeting.

Jen, did you want to introduce yourself?

DR. NADEL: Hi. This is Jen Nadel. I'm a medical officer in the Division of Anesthesiology, Addiction Medicine, and Pain Medicine.

DR. STAFFA: Great.

Jen and I are going to tag team on this. We have the privilege of facilitating a discussion,

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which we are very pumped about because of all of the information we've heard the last couple of days. But the real challenge here is going to be how we are going to pull this all together and actually try to answer some questions that we've tried to draw up, which I'll walk through.

Our goal here is -- inasmuch as it's really important to talk about these issues, and we're really happy that everyone has come together and shared some of the work that they've done -- we really want to try, as best we can, to come out of this and go back to the shop and try to build a research agenda.

That's really our goal, is to work with our federal partners, determine what are the important priorities in the science in this space, and then figure out how we can do our part to try to help support and generate new knowledge that will make MMEs, their calculation and their application, as meaningful and as productive and helpful to the whole situation of pain management, as well as the opioid crisis, if possible.

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So with that in mind, I'm going to be trying to facilitate the discussion by calling on folks and making sure everyone is heard as we walk through the questions.

Jen has the unenviable task of trying to do her best to record and capture a lot of the themes and the points made, and to try to put them into different buckets the best she can. So she'll be coming in and out of the discussion, needing to clarify or to hear more about certain points. So you'll definitely be hearing from both of us.

So to start, I know that the discussion questions were circulated. I'm hoping folks had a chance to look at them prior to the presentations so that you could be thinking about what are the main points that you might want to bring up.

But what I wanted to do is walk through them just to give you an idea of what the questions are going to be, so that you can kind of plan your comments, and then we'll go back and start at the beginning and go through the questions one at a time; although I will apologize in advance.

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We tried our best to carve these out into completely separate and non-overlapping buckets. And yes, I hear you laughing. It was not possible to do that. This is so complex that all of these areas are overlapping. So we do understand that some of these questions may bleed into others, but there are definite foci for some of these questions that I want to make sure you understand.

Just starting to go through them very briefly, in question 1, we really want to start drilling down. We know that in the different application areas of MMEs there may be different knowledge gaps, but there may also be some knowledge gaps that are common to all applications.

We want to discuss and go through them kind of in buckets that focus first on considerations relating to the drugs themselves, and then move on to some of the patient-level factors and information where there might be knowledge gaps, and then be thinking about some of the more population-level gaps that we've heard about, as MMEs are used not just in a patient conversion

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setting, but in more of a public health or surveillance setting.

The second question we want to zoom in on is we're not really asking for specific study designs, but more what types of studies do you see. You've heard some nonclinical work, you've heard clinical work, you've heard claims-based studies; so to give us some ideas of these different areas and what do you see as the kinds of work where we really should be focusing on to get some of the crucial answers in those spaces. So your ideas on that front will be helpful.

Then question 3, we want to make sure that these buckets we've identified in question 1, we want to make sure that we haven't missed anything; so other things that perhaps we haven't focused on or we just haven't thought to include or invite people to present about. So we want to make sure we're not missing anything.

Then we'll roll into questions 4 and 5, and really get more into the conversion tables themselves and what kind of work do people see.

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What are some of the goals of conversion tables? Should there be one common conversion table? Are there certain issues relating to the calculations themselves around conversion where we could target, and to try to figure out where should we be heading in this area that would be the most helpful. So that's questions 4 and 5.

Question 6 is, again, other areas that we want to make sure that we haven't missed anything. And I know in some of the clarifying questions yesterday, a couple folks snuck in some different paradigms or different ways to think about this, so that might actually fall nicely under question 6.

Then finally in 7, I'm thinking we're going to have a rich discussion. We're going to identify a lot of issues, and then in 7, we're really going to ask people to be thinking about how to prioritize; if this was up to you, what do you think are the most important areas to target first?

I know I've come away from these last two days with a new appreciation of even more complexities than I even thought of before. So it

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will be helpful for us, as we develop this research agenda, to actually be able to zoom in and prioritize on areas just to get things started.

So with that in mind, I wanted to make sure we all understood the ground rules. We're going to do what we did before, which is, if you would like to make a comment, raise your hand. Paul Tran will be keeping track of the folks in the order in which they raise their hand, and I'll call on folks.

When I recognize you, if you can unmute yourself and state your name for the record, that will make it easier for the transcriptionist, and then state your comment, and then if you could mute yourself again. And again, if there's a back-and-forth discussion, obviously we'll call on you again.

I wanted to also remind you to put your hand down if you've already contributed your thoughts, but feel free to raise your hand again if you have another thought. Then I wanted to just remind my FDA colleagues that are on the panel, if you also have questions or clarifications you'd like to

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hear, if you'd like to hear more if someone's made a comment, or you're not really following it, or you want to add to it, by all means raise your hand or chime in on the chat, and I'll know that you want to contribute to the discussion as well.

So with that in mind, Jen, anything you wanted to add? Anything I've left out in terms of housekeeping?

DR. NADEL: No. I think that you nailed it and got everything we wanted out there to start.

DR. STAFFA: Great. Okay.

So we're going to start with question 1. And again, I know it's broad, but it's deliberately broad because we want to get the conversation started.

Number one is to discuss any potential knowledge gaps in the science that underlie MMEs across various applications. What we were hoping is to take the approach of these three different areas of the considerations with regard to different drugs or different opioid; considerations with regard to different patient-level factors or

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gaps in the area, again, of any application, whether it's for conversion, or rotation, or whether it's being used as a risk predictor, or other areas.

Then again, in terms of a population level, you've heard a lot of conversations about how MMEs are used not just for individual patients but in populations of patients using claims data to try to identify patients that might be at risk and helping us identify. We'd like to come up with just a list in these different areas of what you think the important gaps are.

So I will stop there and see if anybody would like to get the conversation going, in any of these three areas.

Dr. Fine?

DR. FINE: Great. Well, thank you. Can you hear me alright?

DR. STAFFA: Yes, we sure can.

DR. FINE: Great. Alrighty.

Well, once again this is Perry Fine reporting in from the beautiful Wasatch Front here

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in Salt Lake City, Utah. It's really been a joy to hear some of the in-depth presentations the last few days, and I'm so grateful that the FDA is attacking, if you will, this problem yet again.

To get to some of these questions I thought -- and really to get the discussion started and not to dominate things at all, but just to create some additional context, there were a few things that were not covered, at least, or maybe glossed over -- to create some context that we can then maybe pinpoint more specific issues around these questions; so if you just give me about a minute here to maybe create some of that context.

First, this is not a new problem, and anybody who's been in the field for maybe at least a decade, and longer, knows that this is not the first time that this issue has come up with regards to issues around equianalgesic dose conversion and opioid rotation, et cetera.

It's just that we have really not made much progress, and I think some of the questions and some of the comments maybe I made yesterday sort of

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point to a little bit of that sense of impatience and frustration with some of the false starts we've made, and that I believe and hope that this time around we can make some better progress.

From the historical standpoint, which is not just mere history but has created the foundation for all of what, unfortunately, I believe flawed science -- in other words, a science that has not been built up on a solid foundation of studies that really support the way MMEs have developed and all the issues that have been brought out, is to recall Dr. Ray Hood and others, dating back 30, 40, 50 years, and actually the methodology that was used to try and understand at least analgesic equivalency, which was really the issue, was based upon a basic two-dose, crossover methodology, extrapolating then dose conversion based upon an analgesic equivalency, including different routes of administration.

Built upon that data, which was very good and very sound, it did not apply to the broader and the typical clinical conditions where opioid

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rotation, opioid conversion, and opioid switching -- however we want to term it -- is actually necessary in real-life circumstances. We're not talking exclusively about acute pain, or a single dose, a trauma, or a surgical model, or an animal model. We're talking about protracted use of analgesics and all the variables that therein lie.

So if you've built a house on a faulty foundation, you're not going to end up with a very sturdy house, and I think that's where we find ourselves. And I just wanted to summarize that as coming out from what I heard loud and clearly as conclusory points from the presenters that did an exemplary job of pointing out all the flaws and translating acute and experimental pain models of opioid comparative potency to broader clinical application.

Lastly, I think it goes without saying, except it needs to be said over and over, that there is a true dearth of prospective trials, in most circumstances, that apply to dose equivalency,

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or potency, or dose conversion, in most of the clinical conditions in which we need to apply them, in order to provide not only therapeutic efficacy but safety for patients.

With that as a pretty broad context around some of this discussion, with regards to the first question on the drug considerations, I think it's been pointed out -- and I will just repeat it -- that when we go across opioid subtypes from pure agonists to the various other types of opioids that are now in common use, including partial agonists and mixed-effect agonists -- that is, norepinephrine, uptake inhibition, and so forth; methadone with an NMDA receptor phenomenology -- to try and impute or generalize from the limited data that exist, even amongst the agonists, is a leap and, unfortunately leads to faulty conclusions and problems.

How we deal with that I'm sure we'll be discussing later on. But I just wanted to emphasize that for discussion point 1A. Thank you.

DR. STAFFA: Thank you very much, and thanks

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for the background. It's very helpful for folks who may not have been in this space as long as some others, so thank you.

Dr. Mellon, did you have a comment to make? Could you unmute yourself and just state your name?

DR. MELLON: Certainly. This is Dan Mellon, deputy director for pharmacology and toxicology for the Office of Neuroscience.

As a pharmacologist, I thought it would help to perhaps chime in before we start getting into the patient-level aspects that I will clearly defer to my clinical colleagues' expertise on. But one of the things that I was trying to bring out in the presentation today was that there really is a lot that we just don't know about a lot of these older drugs.

I think the point that Dr. Fine is making, that the ones that seem to cause the most challenge when it comes to trying to compare these are the ones that have mixed pharmacological profiles -- a little bit of serotonin, a little bit of norepinephrine, activity in NMDA -- we know NMDA

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involvement is clearly impacting the degree of tolerance that can show up with these particular compounds, and that can really confound the ability to compare these products.

One of the things I think is worth stressing is that we really don't have a great understanding of the profile, even within the opioid receptor class, for what many of these older products actually bind to.

In a new drug development program, we would not only get very good opioid receptor binding profile and functional data, but we also get a secondary pharmacological screen, and that secondary pharmacological screen can include 60 to 120 different receptors, generally for compounds of this nature, that would be receptors that are located in the central nervous system that very well may help us understand some of the subtle nuances that may be taking place when these products are administered.

As pharmacologists and toxicologists, we leverage that data to try to interpret side effects

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that don't quite look like what we would expect when we look at toxicology studies or we look at pharmacological studies, but we have very little of that for any of the compounds that we've discussed predominantly today.

I think even though it would be very difficult to try to build in and understand the net effect of activation of multiple receptors by these compounds at different doses, the fact that they can alter the way that desensitization can take place, the way that tolerance can develop, I think that's a data gap that really does need to be addressed.

I think in the long run, even though at the end of the day, the clinical data are in terms of understanding the risks going to rule and understanding the types of events that were looking at, understanding that pharmacology helps us interpret that data.

So I would propose that we actually still miss a great deal of information, basic information, about the drugs that we're discussing

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today, and I would hope that at some point we would have an opportunity to build that database and build that foundation of knowledge that hopefully may help contribute to these challenging questions. Thank you.

DR. STAFFA: Thanks a lot for that orienting comment. Yes, I think that's very helpful to remember.

Dr. Bettinger, I believe you were next. Could you unmute yourself and just state your name?

DR. BETTINGER: Absolutely. This is Dr. Jeff Bettinger, pain management, clinical pharmacist up in Saratoga, New York with Saratoga Hospital.

I wanted to bring up a couple of points really piggybacking off of what Dr. Fine just brought up and what Dr. Mellon just brought up, I think especially revolving around this first question of any of these potential knowledge gaps regarding utilization of MME and the application.

I think the first thing that's essential, and what I think we probably all agree on, is we

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need to define in each scenario what the goal is of using the MME calculation. As Dr. Mellon and Dr. Fine were just saying, if the goal is around opioid rotation, for whatever reason -- say someone has developed some tolerance, say there's hyperalgesia, say there are side effects -- then I think a lot of the data that we have is really around the equianalgesic effects of these opioids comparatively.

However, that's very different data than what I think has been happening over the past 10-plus years, where we started to try to use MME and equate different toxicities and different toxicity profiles between these opioids.

The problem is we haven't actually created new data for that. We have in ways, but we haven't studied the equal toxic doses between these different opioids, and it's going to relate to each individual toxicity. So do we want to talk about the abuse liability and the euphoric effects, or do we want to talk about the patient effect, or the respiratory depression effect?

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Those doses, because of what Dr. Mellon had just said, and really what his presentation was about, because of the differences in the internal mechanisms between these drugs and these opioids, that's where we can really see some significant differences.

So I think that's one part of this that maybe we as a group, or going forward, have to address and figure out what is the goal of the MME calculation. Because I think what we will likely find, if we really start to study this going forward, equianalgesic dose in conversion factors may be very different than equal respiratory depression doses, in effect; again, because there are so many differences in individual characteristics of these opioids.

I think that's a huge knowledge gap that we're going to have to address at some point, and that kind of leads me to my next point.

I think the other thing we have to look at, especially from a population level, is what are we looking at in terms of the goals of limiting an

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

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

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

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

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

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

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

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

DR. STAFFA: Thank you, Dr. Bettinger. You're really amplifying these particular drugs that we really need to understand more about, as well as the outcomes other than analgesic potency; you mentioned respiratory depression and others, to be developing more of the science there and not to be assuming the differences we see with analgesia that applies to others, and I think we saw examples of that as well.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. STAFFA: Thank you, Dr. Fine.

Dr. Chidgey, would you like to unmute please, and just state your name and then provide your comment?

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

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

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

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

DR. STAFFA: Thank you so much

Ms. Cowan, did you want to unmute and just state your name and provide your comment?

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

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

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

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

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

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

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

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

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

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

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

Dr. Fine, did you want to jump in here?

DR. FINE: Yes. Penney, thanks for always bringing us back to reality and putting our feet squarely on the earth.

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

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complexity amongst this notion of this construct we call MME.

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

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

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

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settings, to have a broader perspective of how this fits into that.

We can't solve all of the problems at once; we have to deal with them. But we can't pretend that they're not very and powerfully interconnected. So I would hope that one of the takeaways from this workshop would be rapid movement towards an ongoing separate but connected approach towards a fresh look at the construct of debilitating pain, independent from and sometimes connected -- occasionally connected - to issues around substance-abuse and misuse issues, but not conflating the two, which has been done to extraordinarily -- and I will underscore a thousand times, extraordinarily -- perverse ends over the last number of years. Thank you.

DR. STAFFA: Thank you, Dr. Fine.

I believe I see Dr. Sandbrink. Your hand is raised. If you want to unmute yourself, and state your name, and provide your comment?

DR. SANDBRINK: Yes. Friedhelm Sandbrink, Washington, D.C., Veterans Health Administration.

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Thank you very much. I really certainly learned a lot over the last couple days from these excellent presentations.

One thing that comes to mind is that we have to probably separate the tool, which maybe is MME conversion that can be used in clinical practice, from the implementation of this tool as some kind of policy guidance or state regulations.

I feel like from the experience of our healthcare system, when I talk about the risks of opioid prescribing and guidance that we have done in regard to opioid reductions, that we have been very careful of making sure that the patient factors, and the patient interests, and the patient concerns are being included in the discussion and moving away from the actual number of the dosage or whatever the MME calculation is.

On the other hand, as we make adjustments, we need to provide guidance to clinicians of where they are with the medications that they utilize. I think there are conversions that happen every day in clinical practice that are needed, so the

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guidance must be there. But what we really actually learned is we need to probably get much better guidance not just about the analgesia, which is often, from what I understand, the MME is being used for, but when we make a conversion in regard to opioid reduction, it is often more an MME level in regard to preventing withdrawal. So maybe that's the second set. Right?

Then we have an MME level in regard to respiratory depression, and possibly an MME, as we heard, that may differ also in regard to risk of addiction. And it may be related to the different subtypes and obviously whether it's a full or partial agonist, and it ends up being very complicated. For clinical practice, though, what ends up is things are being simplified too much, way too much, but at the same time we have to have some guidance that can be of assistance in clinical practice.

So I feel like maybe we need to emphasize more the limitations of any kind of conversions that we have, whether that's for analgesia, or

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whether that's for respiratory depression, or whether that's for withdrawals, but also keeping in mind, always keeping in mind, that this is just a tool that should not be used in regard to certain regulatory attempts or legislative attempts from a broader perspective; the end of my comment.

DR. STAFFA: Thank you, Dr. Sandbrink.

Dr. Dasgupta, can you unmute yourself, and state your name, and provide your comment?

DR. DASGUPTA: Yes. Good afternoon. This is Nabarun Dasgupta. I think on a population level, there are two things that come to mind, listening to the last few comments here. One is that the large data sets, whether it's claims or PDMPs, don't contain really good patient-level improvement metrics. Sometimes in EHR, we'll get pain scores, but those are instantaneous measures that aren't so sensitive to change. We don't get much in the way of social determinants of health and other things that are confounders, as well as the outcomes that matter to patients. So until those kinds of metrics are in the big databases, I

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think analysts are going to pick what's there and what's convenient, which is ICD-10 coded outcomes and things like that.

The second comment is with regards to evaluation of state-level policy impacts. In North Carolina, we've looked at the STOP Act, which is our state's version of those with prescribing limits and things like that. When we interviewed -- I can't remember how many doctors and other prescribers we interviewed, but it was dozens, not over a hundred, and hospital administrators -- what we heard repeatedly was that the 90 MME number is really convenient as a mnemonic for having a line after which you need to pay little bit more attention.

That sounds kind of reasonable, but the other type of comment that we had was that it's something that the physicians can use to push back on patients they're not comfortable with prescribing higher doses. So it's kind of externalizing the responsibility and saying, hey, my hands are tied, this is the law, this is the

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recommendation. In those situations, it wasn't usually like pain management practitioners, it was more general practice and other specialties.

So I think we can give guidance, we can give instructions, and have all sorts of guidelines and whatever, but at a very human, physician-patient level, there's something kind of psychologically going on here, emotionally going on in that encounter, which I don't know that additional guidance is going to solve.

DR. STAFFA: Thank you, Dr. Dasgupta.

Dr. Zhang, can you unmute yourself, and state your name, and provide your comment?

DR. ZHANG: Thank you. Can you hear me?

DR. STAFFA: Yes, we can.

DR. ZHANG: I think maybe Penney Cowan raised her hand before me. I just want to make sure I didn't jump the line.

DR. STAFFA: I believe we heard from Ms. Cowan, and we can go back to her.

DR. ZHANG: Thank you.

DR. STAFFA: Ms. Cowan, is your hand raised

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again or did you not put it down from before?

MS. COWAN: No, I'm good. I'm done. Thank you. Sorry.

DR. STAFFA: Thank you so much. No, that's alright.

Go ahead, Dr. Zhang. Thank you for being so courteous. Go ahead.

DR. ZHANG: Thank you. This is Kun Zhang from CDC. Just one follow-up and response to a question that, Judy, you asked about, gaps at patient level.

First, the comment is I really enjoyed this discussion in the afternoon; very helpful. I think there are a lot of points, good points, made by the panelists that reflect, unfortunately, there has been a lot of miseducation on the CDC guideline, including certain specific recommendations in the guideline. That's just one quick comment to what we discussed previously.

To your question, Judy, the patient level, the 1B here, I think we focused a lot on opioid rotation and conversion. I'm not sure if this is

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already including opioid initiation, which I think is also an important topic to consider here.

For instance, I know yesterday, several speakers, they all mentioned, including Dr. McPherson - I remember one slide. The first point was to assess whether opioids should be the choice, opioid therapy. I think opioid initiation should be an important topic here, although we know from the data that in the past several years, what we saw that had decreased gradually the most is new opioid initiation, including, for instance, a short-day supply of opioid prescriptions probably from dentists or from ER.

But I just wanted to give an answer to the question you asked. Thank you.

DR. STAFFA: Thank you very much for bringing that up. So you're pointing out the need to better understand when opioids should be initiated, so that's not really an MME calculation. You're suggesting that that's more a consideration?

DR. ZHANG: Including the dosage for initiation.

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

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

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

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

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of these other factors and other issues that are not currently considered in the calculation.

Would that be a fair statement?

DR. BETTINGER: Absolutely. Yes. And I thank you for bringing that up because it is looking at those other functionalities like you said, depression, anxiety, mood, as really Penney alluded to in that introductory presentation, and going back to John Bonica and understanding pain is multifactorial. It affects several different types of things at a lot of different levels for individual patients and their families.

So trying to incorporate more broad outcomes and looking at other things just besides what's the decrease in pain score itself. Absolutely.

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

I'm going to be mean here, and I'm going to pick on Dr. Comer.

Dr. Comer, I'm wondering, since a lot of your work has looked at some of these other outcomes and these other effects, I'm wondering if

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you have any thoughts on some of the clinical studies that might be the natural next steps for some of the work -- that you and your colleagues at the University of Kentucky, Dr. Babalonis as well -- that you guys have conducted.

Do you see clinical studies that might serve as a good next-step here to your work?

DR. COMER: Yes. I've been sitting here thinking about some of the challenges that we face in our work.

DR. STAFFA: And I'm sorry to interrupt. This is, Dr. Comer, right? I just want to say for the record, this is Dr. Comer.

DR. COMER: Yes. This is Sandy.

Shanna and I are both used to doing studies where we try to control things very carefully, do time-effect curves, dose-effect curves, double-blind conditions of dosing parameters and things like that. There are all kinds of ins and outs of doing that kind of research, and we've figured out how to do it.

It's relatively simple to do it in a normal

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healthy volunteer population, even recreational drug users. As Shanna mentioned in her presentation, it's another level of complexity to study people who are physically dependent with opioid-use disorder, but we've kind of worked out the parameters of how to do that.

Working with pain patients is kind of a whole other ball game in the sense, as people have described throughout these two days, that there are so many layers of complexity with that patient population, and trying to get a handle on, at least from my perspective, the abuse liability of opioids in that population is even doubly, triply complicated for a whole bunch of both ethical and scientific reasons.

The ethical reasons are that you have somebody who's telling you that they're in chronic pain, so from an ethics perspective, you don't want to put them on nothing. So you have to have them on a medication that we feel would be successful in controlling their pain, so we've done that with buprenorphine, for example. But then when you do

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that, trying to understand the abuse liability of an opioid on top of that gets really complicated.

We tried to do that. We recruited people who had chronic pain and were misusing their opioids, and we put them on sublingual buprenorphine 4 times a day. Then we thought, okay, if we can push the dose high enough, we can look at the abuse liability of oxycodone under those conditions, for example, with the thinking that maybe clinically it would be analogous to somebody using oxycodone as a breakthrough medication.

But what we found was that all of the doses of buprenorphine that we were testing completely blocked the effects of oxycodone, and we were actually also comparing it to morphine. We went up to an acute dose of 360 milligrams of morphine and got no effect of morphine at all.

It was just like, okay, that's a ridiculously high dose, and we gave up to 180 milligrams acutely of oxycodone. Same thing; there were no ratings of drug liking, no ratings of

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feeling high, nothing, and they were only maintained on 4 milligrams of sublingual buprenorphine. So it's like we were scratching our heads, how do we do this? How do we do this kind of research?

Then on top of that, the scientific complications are that these patients who have chronic pain, who are misusing their opioids -- as I kind of touched on this earlier today -- they may be taking the opioids for two reasons. One is that they want to get high, so that's the positive reinforcing effects of these drugs, but then also -- and someone else touched on this as well -- they're using it to remove the pain.

So we had to come up with a whole list of questions that we asked that said, "I like the drug because it removes my pain. I like the drug because I felt that euphoric effect." So it adds a whole other level of assessment that we haven't had to do before. It's tough. I know it's a long-winded answer to your question, but --

DR. STAFFA: Oh, no. It's helpful to hear

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some of the challenges and complexities from people who do this work. So yes, it's not straightforward. Thank you for sharing that.

Dr. Babalonis, did you have anything to add to that?

(No audible response.)

DR. STAFFA: Okay. Well, please raise your hand if any other thoughts come to mind.

Dr. Fine, did you want to weigh in on this topic or did you have a different topic to discuss?

DR. FINE: Yes. I wanted to sort of keep the discussion going. I guess I'm finding myself in that respondent situation where I'm stimulated by all these comments, and it makes me think of other things.

First of all, on the host presenter chat, there are many other papers we could cite, but I threw in three of them that date back 10-12 years ago. And the reason I did was because there's certainly some new science, and we need to understand how to integrate that. But a lot of the questions we're asking, the focus is really more

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sociology. The pharmacology is complex enough, but what's really complicated is people and the whole person.

We don't need to fully reinvent the wheel. With some of these questions, the question you've got is question number 2 and has been addressed in the past in various forums, including at the FDA in 2013 at that meeting. I don't know if anybody else was -- I can't remember who was there, other than myself.

That sort of didn't go anywhere, and I don't know what happened with those proceedings. But there certainly has been a lot written about what do we need to know and how would we proceed to knowing it. So I at least wanted to provide a lot of those thoughts that have been in published form to reinvent the wheel.

Dr. Comer really underscores this question why. We really have not put in the time or effort to understand these various cohorts of individuals, who we call patients, who behave in a whole host of different ways and they're motivated by a whole

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host of different things. Sometimes they're overlapping; that is they're motivated by pain. Some people end up being motivated by drug use that turns into misuse and abuse that has nothing to do with pain, but sometimes it's overlapping. They may be very different or overlapping cohorts of patients, and we have not adequately understood that.

In my own personal experience and practice for almost 40 years, we maintain an interdisciplinary pain management approach here, which has been, nigh, almost impossible to do, but we struggled to do it. We take all those individual aspects of people -- sort of the biopsychosocial/spiritual model -- very seriously and try to integrate all that.

But what remains is there is a population of individuals, without using opioids as a tool, that would not have near any kind of quality of life or functionality. And some of these patients are on relatively modest doses of opioids, and some are on what we would call maybe intermediate, and others,

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what might be called high doses of opioids, and they may be absolutely indistinguishable from each other in their overall behavior outcomes.

Some of these patients we've been following for 25 or up to 30 years, and they don't dose escalate. They are adherent to the plan of care. They appear, in terms of how they behave and function in their lives, like most of the people on this conference call. They don't have a use disorder. They are not debilitated by psychological/psychiatric issues once their pain is managed effectively, and opioids become a critically important part of that, and they seem to manage well.

We don't understand the differences amongst these individuals and others who have problematic use behaviors, or have adherence problems, or would start out with a use disorder, and then we still have to manage and maintain pain relief one way.

The methodology has really not been well established of how to sort out those cohorts, how to separate out and understand those variables,

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both at the pharmacological level and the sociological level. Although there are ideas, I don't think we're going to come to any great conclusions here today; it's a deep issue.

But one thing that's absolutely for sure, there has been no investment in doing this, and it's unlikely that -- the pharmaceutical companies are not motivated to do this. They're not rewarded for that. The kind of information that comes into FDA, I know in reviewing those data, doesn't ever really get to that in terms of phase 1, 2, and 3 trials for drug approval.

Until NIH takes this seriously and makes an investment in a methodology, and is willing to commit to doing the kind of methodologically sound trials that would allow us to understand and ferret out the differences and what makes people behave differently under different circumstances, I think we're going to be spinning in circles.

I'm not nihilistic about this. I just think that even a registry model, which has come up as an alternative, sifting through and sorting that out,

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I'm not sure we've got the computing power or the insight to enter in those variables, certainly for any typical clinical record as of yet, without capturing a cohort of individuals.

For instance, on high-dose opioid therapy, who appear to be functioning very well, making them a discernible study group and trying to understand why they are the way they are, as an example.

DR. STAFFA: Thank you, Dr. Fine.

DR. FINE: Thanks.

DR. STAFFA: Dr. Comer, did you want to make another comment?

DR. COMER: I was just going to say that a number of years ago, the IMMPACT group, the one led by Dennis Turk and Bob Dworkin, they organized I think it was a two-day meeting, bringing together people with expertise in pain and people with expertise in abuse liability, and it was a really interesting interaction because we were trying to get a handle on how do you assess the abuse liability of opioids in patients with pain.

One of the things that I took away from it

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is like, wow, we're really speaking different languages. I guess I would just want to recommend that that would be something I think that would be helpful to the field, is if the two areas talk more.

I know we've tried to do that, and that's what Bob and Dennis were trying to accomplish. If we can do that successfully, I think that that would help move us forward in terms of the science.

DR. STAFFA: Right, right. Sometimes it takes more than one try to get two groups of people, one speaking Greek and one speaking Latin, to actually move ahead. I agree.

Since Dr. Fine had brought up NIH, I have to take that opportunity to see if our colleagues from NIDA have anything they wanted to jump in and add, or speak to, or think about as we consider this idea of these kinds of clinical studies, perhaps looking at abuse liability and patients with chronic pain.

Any thoughts on that from Dr. McCann or Dr. White?

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DR. McCANN: Yes. Hi. This is Dave McCann. I have to say I work on the medication development side of things and working to develop new drug addiction treatment products, and overdose treatments, and so forth. I have learned an awful lot during this past day and a half.

It's just slightly off topic, but one thing that I have to mention is that, really, in the long run, not having to deal with these issues and having safer more effective analgesics that are less addictive, that has to be one of our long-term goals, and we are doing a lot in that direction.

Unfortunately, it takes quite a while for those new products to come to market, but a lot has begun with the increased funds that were set aside for the NIH HEAL Initiative, not just for addiction treatment, but working to develop new analgesics that won't have this type of baggage; that won't put us in this kind of situation.

That doesn't really directly address the question of talking about clinical trial design and dealing with these MMEs, but I think it's got to

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give some people hope up there that we won't be in this situation ten years from now.

DR. STAFFA: Thank you, and thank you for making us aware and reminding us of that important work that's going on under the HEAL Initiative.

Dr. Comer, did you have another comment to make on this topic?

DR. COMER: Yes, just a response to Dave's comment. This is Sandy Comer.

Thanks for reminding us about the HEAL effort in this direction. I also attended the HEAL investigators meeting very recently. I was excited about this one medication that we're working with, from the perspective of treatment medication for opioid-use disorder. It has this really interesting pharmacology that has an opioid component and serotonin and norepinephrine components as well. It produces analgesic effects in preclinical models, but tolerance doesn't seem to develop to it or physical dependence.

It's kind of a unique molecule, but it could be potentially used for treating pain as well. But

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it was clear from the discussion at the meeting that they're not interested in funding anything that has any kind of opioid component. Even in both rodents and primates, this substance doesn't have abuse liability. So it's just like, well, we're kind of stuck.

DR. McCANN: Well, given that NIH is a very large group, because one group isn't interested, it doesn't mean you won't be supported by another part. I think a lot of the analgesic work that is opioid related tends to come to NIDA, and many of the projects that are not, end up going to NINDS.

So there are other institutes. One group may be more interested in one project than another, but I certainly wouldn't give up on a product like that moving forward for analgesia just because you got some negative comments. When an application comes into NIH, they'll decide which institute it goes to, and I would keep that in mind. There's still another direction it might be able to go.

But it is very exciting, the number of different approaches that are being taken. There's

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one that actually predates HEAL. Many years ago, we worked with the folks in the Dental Institute to move a compound along. It's called resiniferatoxin. I can't figure out how to type into the main box here or I'd spell that for you all. It's also sometimes abbreviated RTX.

We worked to help get that into the initial clinical testing, and then there's a private sector pharma company working on moving it forward. They're actually looking at injecting it into the knees in folks with severe arthritis, so it seems to be helping quite a bit. This is something that's not going to affect respiration at all.

So it's just one example. There are many approaches that I think, again, ten years from now, hopefully we'll have a lot less need to use opioids that are so dangerous.

DR. STAFFA: Thank you.

And just for the record, that was Dr. McCann speaking. I just want to make sure they appropriately attribute those remarks, Dr. McCann.

DR. McCANN: Oh, that's right.

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

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

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

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

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Comer, these are very important points. But I think there's also a reason -- I'm not a psychologist, I don't even play one on TV, but I've hung around them long enough now to maybe be a little bit aware of what motivates people; if not myself. As Dave McCann said, the NIH is a very big organization, and there have been attempts at bringing groups together.

But maybe as more of a political comment than anything, there was tremendous resistance and has never been an adequate response to the huge public health problem, if you will, if you want to call it a problem, of millions of people, tens of millions of people, at extraordinary costs. In fact, the last effort to look at this attributed something on the order of between $800 billion and a trillion dollars of costs related to intractable or debilitating pain in this country, which I think added up was greater than heart disease, diabetes, and cancer combined.

Yet, there still is no institute of pain or either clinical research within NIH. There is the

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IPRCC, the Interagency Pain Research Coordination Advisory Committee, but it's an advisory committee. And there are some brilliant people and very dedicated people on that, but until there's a championing, motivating, this is your daily work, this is your career, this is what your ego requires, et cetera, I think we're not going to get to that place that we all sort of say we want to get -- no less able -- and connect the bridges between NIDA and this prophetic institute of pain.

So I think there's very good reason we have not progressed much in the last ten years over this, and we have more questions than answers. Maybe that's something that could come out of FDA, as a branch of Health and Human Services, is an acknowledgment that until such time as we truly commit whole hog, and put our egos, and our professionalism, and our careers, and have committed resources behind it, maybe we're going to continue to spin wheels.

Again, I'm not a nihilist; I'm highly optimistic. But there's a reason that IMMPACT

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never went forward, and HEAL is all about non-opioid, and so forth.

I just had to smile, Dave, at your comment about maybe ten years from now. I remember in my typical impassioned way, as you can sort of hear it, standing up at several meetings, including FDA meetings, and the Office of the White House's National Drug Policy, and so forth, more than ten years ago, saying, "Ten years from now, we won't have to have these discussions because I know we'll have drugs that will not have abuse liability, but for the meantime, we need to get good at what we have."

Well, 10, 12, 15 years has passed, and we're still there. I'm afraid if we don't do something more focused and intentional, we'll still be here in 2030, having the same discussions. That's my grievance.

DR. McCANN: This is Dave McCann jumping in. I agree. I think ten years seems like a long time when it's in the future, but then it goes by really quick, and you're right back where you were.

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I just have to say that, personally, I agree it would be fantastic if we had a pain institute. I see even communication challenges within an institute, between divisions and so forth. While we do have a trans-NIH pain initiative group, representatives from different institutes getting together to focus on pain, I think it would be fantastic if we had a pain institute.

I understand that there is a limit to the number of institutes and centers that NIH is allowed to have, and I think that may be what's holding it back. You just look at the list and say which one do you cross off to create a new one. Maybe that needs to change.

DR. STAFFA: Great. Thanks for taking that one, Dr. McCann.

Okay. I'm going to move us over to question 3. And again, if there are other thoughts of creative or innovative types of studies, or designs, or issues you'd like to raise or you want to bring up in later questions, we can certainly revisit that.

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Question 3, I guess I want to kind of probe a little bit on some of the factors we didn't talk about a lot in our previous discussions. We kind of touched on, I think, a lot of the drug considerations, the issues around drugs, like buprenorphine, and tapentadol, and methadone, and some of the outcomes beyond analgesia as an outcome, and some of the other outcomes that are worth comparing and understanding different opioids and their relationship to each other on.

But I wanted to just get folks' thoughts about what are some of the other key factors that we heard about a lot yesterday and again today about patient and population levels, issues that we need to make sure are brought into some of these studies, whether they're preclinical studies, whether they're nonclinical studies, or whether there are some of the studies we talked about in patients with chronic pain and those kinds of populations, too.

I think folks have brought up the point that these are populations that have not really been

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adequately studied in terms of understanding some of the outcomes here, and really understanding what happens to patients over time and what some of the risks may or may not be.

Any other thoughts folks would like to add in terms of priorities for our research agenda in those areas, things we haven't yet touched on that might have been brought up in the talks you've heard, or not brought up, but occurred to you based on the work that you've done?

Dr. McPherson, would you like to unmute yourself and state your name and make your comment?

DR. McPHERSON: Lynn McPherson, University of Maryland. It just occurs to me that perhaps we should be considering doing some qualitative research along with this and looking at the perceptions of prescribers.

I think what's really made things kind of hit the fan is prescribers are scared to death to write for opioids and they're so fearful of these limits, even though the CDC is very clear this is guidance. It's not carved into a tablet brought

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down from the mountain, but people are very fearful and patients are paying the price. So perhaps doing some qualitative research in this area would be beneficial. That's it.

DR. STAFFA: Thank you very much. That's very helpful.

Do folks have other thoughts they want to contribute? That's a little different from what we've heard, so yes, that's something we can definitely bring in, and more in the social science area.

Dr. Chidgey, would you like to state your name and provide your comment?

DR. CHIDGEY: Yes. This is Brooke Chidgey from UNC. I think that makes a lot of sense. I know as a pain provider myself and prescriber, what we see is a lot of the physicians and prescribers in the community just refusing to prescribe opioids altogether. And while the CDC guidelines, as you mentioned, are just a guideline, it's really been taken much further than that, and further than intended, and MMEs being used by medical boards,

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for example, and providers are scared.

I certainly have been afraid. When I do what I think is right, I do wonder sometimes am I going to get in trouble for what I'm doing, even though I think it's very medically appropriate and sound, but because of the ramifications that go along with prescribing a high-dose opioid and it being flagged. Thank you.

DR. STAFFA: Thank you. Yes, those are very good points.

Dr. Comer, would you like to make a comment here?

DR. COMER: Yes, just a suggestion for research questions. It would be really interesting, I think, to measure MMEs as they relate to other endpoints like quality of life, and drug craving, and some of these endpoints that I don't think we pay enough attention to, because I would imagine that quality of life will go down as the MME goes down.

So just a thought; I don't know. These patients seem like they're not functioning very

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well at all with these lower doses that are being prescribed nowadays.

DR. STAFFA: Right. No, that's actually a very good thought.

For the transcriptionist, that was Dr. Comer.

I also wonder, as we think about it, that I'm intrigued by the idea of trying to understand better what prescribers are thinking, and the pressures they're under, and articulating that. I'm wondering if folks could think about whether there might be any value -- I know that there were some conversations yesterday about getting pharmacists more broadly involved in these issues, of having that expertise more broadly brought into pain management in a more global way to provide some of the insights into patient care that we heard Dr. Fudin, Dr. McPherson, and others discuss of how important that role is. I wonder if there might be studies that could be done to demonstrate the value of that in different environments.

Let's see. Let me go back. I believe,

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Dr. Fine, you were next.

DR. FINE: Yes. I wanted to pick up on that theme of -- and every time Sandy Comer talks, I always think about what's this interface between people living with pain, but also what are some of the other affective or motivational issues around their behaviors around medication use.

I'll just give an example, and I'd love to hear people's comments about this. It's a very typical patient. It's sort of tied to a prototypical patient, so I don't give any confidential or patient-specific information.

Let's say a woman with a very severe or debilitating chronic pain has both neuropathic and musculoskeletal components to it. There are no interventional therapies that have proved helpful, underwent a lot of cognitive behavioral therapy, and is very good at maintaining and managing her diet, exercise, behavioral issues, and insight into mindfulness, and all the kinds of things that are helpful and all, but was able to, and has been able to, essentially lead a normal life, including a

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professional normal life, up to the point of retirement a few years ago, say, using a 100 milligrams of extended-release morphine every 8 hours around the clock and 30 milligrams of morphine, up to 3 doses a day, for so-called breakthrough pain, and has been fully adherent and adheres strongly to urine drug testing, controlled substance database checks, and that kind of stuff.

The question I've been asking myself for the last 20 years, being involved in her care, is how much of the additional opioid, other than the around-the-clock opioid, is used to manage something other than an end-of-dose failure, or resurgence of pain, or some perceived reduction in blood levels that leads to -- she says what's motivating is that when she takes this, it's because she has more pain. But is that because there's a little more stress, a little more anxiety, a little more sleeplessness, something else that enters into everybody's lives, or is it a subliminal perception of a slowly but insidious abstinence and craving? Is it a reduction in

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positive mood that's been drug-induced over time? There's no evidence of hyperalgesia going on that's discernible.

But how do we -- and this goes back to that question that came up after -- gosh, I can't remember -- the talk that ended with the slide that had the green and red lines on it, trying to discern the difference between substance misuse, abuse, and motivations for that versus control of pain, versus the management of other affective, or emotional, or psychological phenomenology.

So that's a question wrapped up in a case example, but I would love to hear you all's thoughts about that. How would we even go about studying something like that to make sense of this without either bifurcating patients into they're drug seeking, or they're pain seeking, or pain-relief seeking? There seems to be a lot of gray in between that we have not been able to -- or haven't really discussed much.

DR. STAFFA: Thank you, Dr. Fine.

If others have comments on that, please do

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

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

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

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

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

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

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

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

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drastically. If we look at studies on education, not too, too much has changed in the realm of overall education at any healthcare professional level around opioids, around pain disorders.

So I think those are things that we could continue to look at, and even take it to almost a grassroots level with education resources. That could be something headed by the FDA, the CDC, and almost thinking of the realm of pharmaceutical companies, the way they, especially in the past, go into physician offices or hospitals and set up CE programs directly to -- again, different types of clinicians; I think if the government began to maybe take some of those steps and, again, look at where the education level is and where it could improve in terms of comfortability.

I think that actually ties in, again, to another role of the pharmacists. It's funny that Dr. McPherson said she used to work in primary care. That's actually what I do. I work across seven different primary care clinics, about 30 different primary care providers, and I

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essentially help co-manage pain patients. I see them. Oftentimes, I follow up with them on my own, me by myself.

I certainly learned under Dr. Fudin, who was of course on yesterday. You tend to be much more comfortable around opioid use in terms of how do we monitor, what questions to ask, even how to approach those conversations with patients, whether they're good conversations or difficult conversations.

So I think that's a role of a pharmacist that's more unique, but I think that can be drastically needed, too. We do often think of a pharmacist at the community setting, the CVS, Walgreens, but there are a lot of pharmacists that practice in clinical settings as well that have, like myself, residency experience with different types of practitioners, learning under psychiatrists, and psychologists, and neurologists, and substance-abuse counselors.

So I think there certainly is a component of underutilization, still, and it comes back to

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billing and other things. But looking at those types of underutilized resources and ways we can improve care by utilizing those resources well, I think could help when we're looking at these types of clinical studies and outcomes. Thank you.

DR. STAFFA: Alright. Thank you for that comment, and I agree with you. In fact, when I was at the Rx Opioid and Heroin Summit earlier this year -- well, I wasn't there actually, but when I participated virtually, there were a number of studies of looking and trying to understand the needs of community pharmacists in this area.

It was looking more at naloxone provision and dispensing, but it was clear that community pharmacists may be in need of some education in this space, and perhaps that may be an area where we can explore studies to try to understand what kinds of education and how it might be most effective in this space.

Dr. Zhang, would you like to make a comment?

DR. ZHANG: Thank you. This is Kun Zhang from CDC. I think we all share some great ideas,

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and I just want to piggyback on a couple of them, for instance, conducting more quality studies and assessing comfortability level of prescribers.

I just want to add, based on some preliminary data we have, one interesting thing we haven't touched is we observed a 20 percent increase in nurse practitioner/prescriber of opioids between 2016 and 2019. Of course, there are decreases in other types of specialties for prescribing opioids.

I think that's an interesting data point, what was driving that and also who these programs/practitioners work for, including nurse practitioners and physician assistants. Of course, from the data, we cannot tell whether they work for primary care, or pain medicine, or surgeons. Unfortunately, we don't have that information, but I think that warrants additional investigation.

The second comment I want to go back to the question on the slide. In addition to MME, at a patient level, I think it's also important to do more research around the specific indication for

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prescribing opioids, which is hard to tell from an observational study or an ideological study. It's very hard to figure that out from claims data.

I think it's important to differentiate what the drug is prescribed for at an MME level, probably by the indications of whether it's for some surgical procedure, or a certain type of chronic pain, or even a migraine. I don't think we have good data points on that. That's another area, I think, back to the question on the slide, that warrants additional research and further investigation. Thank you.

DR. STAFFA: Thank you very much for sharing that.

I wanted to just chime in. Indication, I think bringing that up, it is a real challenge, especially when one's looking at big data, which is often the way we can study and examine what's happening in populations. I think perhaps if there's a way -- I know in drug safety, for years we've often supported work to try to do what we call validation work to try to understand how often

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claims, or charges -- it's often billing data -- are actually reflecting the actual condition behind the billing claim in the patient to make sure that we are looking at the drug safety outcome that we think we're looking at.

I'm wondering if some of that work might also be done to develop algorithms to better understand how different indications appear in claims data, because I think particularly in patients who have chronic pain, those can be rather complex, and not simply a single code but perhaps more of an algorithm. So that is an area that certainly could be --

DR. ZHANG: Yes, exactly. I agree.

DR. STAFFA: -- a science we could study.

DR. ZHANG: Thank you.

DR. STAFFA: Thank you, Dr. Zhang.

Dr. Parkinson, did you want to make a comment?

DR. PARKINSON: Yes. This is Dr. Parkinson. Just quick to go back to the comment about using pharmacists, in the MHRA, and just generally in the

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UK, we're really encouraging the use of pharmacists. For us, the education is the real factor here, and we want to try and increase education for pharmacists, as well as patients. Patients need to know, too.

The pharmacists are basically there on the front line, so they're able to actually give more information to the patient, which they might actually have forgotten when they've seen their doctor.

Pharmacists are also able to see whether that person has been in more than they should really have been. They're able to shop. They're able to see if a patient's a real person or if it's actually someone who is just becoming dependent, or overusing or something, and they're able to then go back and say, "Well, you need to talk to your doctor," or one thing or another.

Within the UK, we're definitely trying to push the responsibility, or we're recognizing that they have a level of knowledge that sometimes the primary care physician probably might not have just

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because they see these patients, or they see the area or the people that are coming through, and they're familiar with a particular opioid or medicine that they're having.

Physicians change and they move around. Well, the same could be said for a pharmacist, but they have a very specific educational base, which is kind of different. So we are supporting that. That's something in which we're trying to push and trying to create more education around. Thank you.

DR. STAFFA: Thank you for sharing. It helps to know that that's an issue that you guys are also working on.

I don't know if you have the same challenges in the UK, but here, pharmacists are often very challenged by the pressures of prescription volume, particularly those who work in large busy stores. It can often be challenging to find time. And as was brought up yesterday, pharmacists are often not paid for their professional services in different areas, and they've become particularly busy as they've become vaccination sites during COVID of

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course.
So I think we would have to try to keep those pragmatic concerns in mind as we think about that and explore that as a topic for understanding better what role they might be able to play.
Dr. Dasgupta, did you have another comment on this topic?
DR. DASGUPTA: Just a quick one in response to Dr. Zhang's observation of the increased number of unique prescribers. I think that is directly attributable to nurse practitioners being allowed to prescribe. I think data that I've seen from late 2019, I think early 2020, was that nurse practitioners now prescribe more extended-release opioids than MDs or other physicians do, in terms of number of prescriptions.
So I think that's been a very big change, but I think it's pretty consistent across the country and linearly observable from the point at which those DEA regs were liberalized.
DR. STAFFA: Great. Thanks for those insights.

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I think, as the chair's prerogative, I'm going to go ahead and suggest that we take our 10-minute break now before we move into questions 4 and 5, which are kind of related. These are going to be tough. These are focused back on more of the MME calculations, and the tables, and the references.
So I want you to rest up, grab your cup of coffee, and we'll see you back here at 3:25. Thanks so much.
(Whereupon, at 3:16 p.m., a recess was taken.)
DR. STAFFA: Welcome back, everybody. I hope you got your coffee and stretched your legs. Those were actually the easy questions we dealt with already. Now we'll get to the really hard ones.
Going back to a lot of what we heard, mostly yesterday, are the real challenges of having so many different conversion tables, and files, and calculators. I wanted to just have folks discuss, do we need a gold standard reference table, and

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what would we need to do to develop that?
If we were to be able to do something like that, what do you think that the purpose for that would be? What is feasible to use this kind of a gold standard reference table? What kind of benefit could we gain from it were we to go in that direction?
We talked a lot about trying to understand a lot of the concepts. The first three questions, we talked a lot about trying to learn more about a lot of the concepts that are not addressed by MME alone. Is there a value that we could address with such a reference table, and what might it be?
So if folks have thoughts about that?
(No response.)
DR. STAFFA: Don't all rush in at once.
Dr. McPherson, I knew I could count on you to get the conversation going here. Go ahead, please.
DR. McPHERSON: Absolutely. Lynn McPherson.
I think this question begs a bigger question. Are you talking about calculating MMEs

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for limits by the insurance company or the state, or are you talking about patient care? That's the end of my question.
DR. STAFFA: I think here we're talking, at this point for this question, the reference would be used in patient care, because I think that's where a lot of these online calculators are currently. Let's start there, at least. Let's focus on that need.
DR. McPHERSON: Can I continue my comment, then?
DR. STAFFA: Please do.
DR. McPHERSON: Okay. Still Lynn McPherson here.
I think the table, while certainly a best practice, evidence-based table certainly is the way to go, is only part of the ball game. We have to teach people how to interpret the data that comes out of that, otherwise we're just doing, as I said, step 3 out of that 5-step process. That's it.
DR. STAFFA: Thank you.
Dr. Chai, did you want to make a comment

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here?
DR. CHAI: Yes. I just wanted to build on what Dr. McPherson was asking. This is purposely written a little bit vague because it's a recognition of the current state of things, that maybe there's an overapplication or misapplication of tables for many different purposes.
So this is more about can we talk more about what's happening now. What can we say about advancing in this space in terms of science and what is possible?
DR. STAFFA: Okay. Thanks.
For the record, that was Grace Chai. Thanks for clarifying that, Grace.
We started with conversion, but this question is clearly open to the use of these kinds of tables and calculators for other purposes and for other outcomes.
Dr. Fine, would you like to add to that?
DR. FINE: Sure. I want to preface this by saying I'm not being a gadfly here. I really believe -- and I think it's supported by all the

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presentations -- that we recognize the limitations of these tables, as well as the extraordinary variability and standard errors that exists within the populations studied.
I think specifically one table that was shown was the transdermal fentanyl data, for instance, where you see mean blood levels for any given dose, but the variability is just extraordinarily high and clinically consequential to the point where, in fact, it turns out the mean levels don't apply to any given individual. In other words, one size does necessarily not fit all; one size fits none. I think what we've been trying to do is -- to put it as a good, close colleague of mine said -- "put a round peg in a square hole."
So my comment, really, which I think hopefully triggers some discussion here, is even the term "MME" is a misnomer, based upon some faulty premises, as we talked about earlier at the very beginning of today's discussion. But we have to do something. We have to offer up something, for both research purposes and for population

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purpose, to understand epidemiologically what's going on. I appreciate there is a great need for that, but especially a need for individual patient care.
I think we've gotten hijacked by the regulatory environment and by policy and political purposes. I won't even begin to get into the opioid litigation, which has driven and perverted so much of what's been going on. And I appreciate comments by Dr. Chidgey and others, who have alluded to those issues, and Penney Cowan, about the fears of prescribers, many of which are really valid fears. It's not paranoia; it is great concern.
In any case, what can we do to address these issues but without pretending that this is good science rather than faulty? I'm going to just throw out a thought maybe you're free to chew on, and that is, instead of morphine milligram equivalents, I think what we really should be talking about in a nonclinical world -- that is research, not clinical care -- is experimental

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relative potency, because that's all I think we're really trying to figure out here.
What is the relative potency in terms of affecting a given efficacy outcome of one chemical versus another, but recognizing that it's all experimental because of the nature of the methodology that got us to these tables in the first place?
We have not had large, prospective cohort studies with all the variables that we've talked about. So in the nonclinical research world, it's really about experimental relative potency, and in the clinical-use world -- practices such as mine, where I have to make day-to-day decisions, either in my clinic, in the hospital, and on the palliative care service, and the home-based hospice service -- what do I turn to? How do I teach my colleagues? How do I teach my fellows, residents, et cetera?
I need something as a starting point, and we're going to get to further discussion about how to use this practically and safely. But I think

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

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

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

Dr. Bettinger, I think you were next.

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

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

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

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

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

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

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

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DR. STAFFA: Thank you.

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

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

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

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

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comparing some of that, specifically how, I think there are probably a number of ways to do it.

I think the other approach is, again, let's try to take a look at potential different risk factors, so those clinical endpoints that you were talking about. One of them, which I think of course has to do with overdose is respiratory depression.

What is the risk of respiratory depression, or very specific, CO2 accumulation in someone that's been maintained on MS Contin, 45 milligrams twice a day for ten years, versus who was otherwise healthy, doesn't have any respiratory ailments, and doesn't have any other risk factors, versus what is the respiratory risk?

What is the CO2 impact or, again, the suppression of our breathing ability? What is that compared to someone who's on IR morphine, 15 milligrams twice a day or 3 times a day, a much lower dose, yet they have underlying COPD, on chronic oxygen, with high blood pressure, and has had multiple heart attacks in the past, and

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strokes?

So I think looking at those very specific clinical endpoints, and maybe there's a way to do it and maybe there's not. But I think that's one way, especially around these MME calculators, talking about the potency of these opioids, again, assessing it and different clinical effects, that's one way we could do it.

Again, not saying it would be easy, as Dr. Comer pointed out a few questions ago about the abuse liability clinical endpoint. None of this is easy to look at. But I think it's important to recognize we at least try to start making these distinctions, because, again, the population being affected the most by a lot of these policies, and a lot of these changes in perceptions and comfortability level with opioid prescribing, are chronic pain patients, most of whom do not have substance-use concerns and do not necessarily have respiratory concerns.

So again, that's some of the examples I was thinking, but I don't know if that answers your question wholly, Dr. Staffa.

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DR. STAFFA: Yes. Yes, it does. Thank you.

DR. BETTINGER: Okay. Perfect.

DR. STAFFA: Thank you for providing a little bit more detail around that. Thank you very much.

DR. BETTINGER: No problem.

DR. STAFFA: Dr. Sandbrink, did you want to weigh in here?

DR. SANDBRINK: Yes. Friedhelm Sandbrink here, Veterans Health Administration, Washington, D.C.

Many have said this very eloquently here already a little bit earlier, but we do need these tools. I think the conversion tables that we have, whether that's a reference table that is being provided as an app or in any other way, I think these tools, among others, are really needed.

I think seeing all the different tools out there, it's just a reflection of how important they play as a role in our clinical care. I think the clinicians need these tools. I think we have to be

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just a little bit more honest about it, that while there are many out there, we've still kept it relatively simple.

We've had these conversion tables. They don't take into account necessarily whether this is for acute or chronic care; whether this is for lower or for higher dosages. Yes, we do make adjustments for different formulations, i.e., PO versus IV, but we presume this to be across the board for all the characteristics an opioid medication has.

But we will need probably specific tables for the analgesia, as was mentioned, and then maybe for the ability to prevent the withdrawals, and maybe for the respiratory depression specifically; and those can be separated, and there are better reference tables that may be needed as a backup and at the same time some kind of note that basically comes with all of these conversions that indicates the limitations for what their specific purpose is, for what this is that is being addressed.

I think having a gold standard is an idea.

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If there's some kind of published official conversion, I think people would love that. Certainly, it comes obviously with risks in regard to is this really the best one or is there an overinterpretation of the value of this and not the recognition of the limitation.

But I want to encourage the FDA, as well as others in the federal government, to make sure that we provide this information and these tools out there to the field somehow. Thank you.

DR. STAFFA: Thank you, Dr. Sandbrink. You're kind of harkening back to some of the points that Dr. McPherson made, that maybe we're in a zone where we're oversimplifying and that perhaps developing a gold standard table might contribute to that. But maybe the more important thing is maybe we need multiple tables for different outcomes with appropriate citation of limitations, but also the added information of how you interpret those values of what you get out of there and what are the important other factors that will influence your ultimate decision about dose conversion or

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rotation. I think those are some very good points that you've brought up.

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

DR. COMER: Yes. I guess to echo what Dr. Sandbrink was just saying, this is what I was trying to convey in my presentation.

I am all for using an endpoint like ED50s, for example, to calculate the relative potency of the range of different drugs. I think that's a step in the right direction. But just a word of caution, those ED50s are subject to a whole host of caveats: how intense is the pain; what route of administration is used; what level of physical dependence, if any, the person has. I completely agree with what he was saying. It would be helpful, I think, to have tables like this as long as we include those caveats there.

Also, just to echo I think it was Dr. Bettinger who was saying incorporating, as well, in these tables of relative potency not only analgesic responses, but also toxic effects; so this is the dose that produces this level of

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respiratory depression, so it's the you have to be careful kind of thing. So you have multiple tables for these kinds of effects that are sort of all interrelated.

DR. STAFFA: Right. I think your work really highlighted some of the differences between the analgesia potency and some of these other outcomes, so I think that's really a fair point. Thank you.

Dr. Fine, did you have another comment to make here?

DR. FINE: Yes, thank you.

Dr. Bettinger went into the toxicology and respiratory depressant mode on some of the clinical effects, but I would sort of supplement the list. If you look at most of the reasons -- and this has been pretty well studied by not only myself but many others -- of why do people need to - I'm speaking now specifically about clinical care and switching from one opioid to another, either so-called opioid rotation or conversion. When there's either insufficient analgesia, excessive

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adverse effects, or the route of administration needs to be changed, there's a concern about excessive, or tolerance developing, or potentially a hypothesis around hyperalgesia.

These are the clinical circumstances that, day to day, an individual who's on a given dose, would potentially need to be switched to another dose, and there are a host of others, but those are sort of the top-of-my-mind lists.

The emphasis has always been in the literature -- dating back to when people like myself, and Lynn McPherson, and Lynn Webster, and others who have contributed, Russ Portnoy, and others who have contributed, to studies hypothesizing certain tools and techniques -- to do this safely and effectively. The consideration has always been safety first; that is, you don't want to induce respiratory depression. People can tolerate virtually everything but that. That is obviously the coup de grace.

So the methodologies we've used -- and these have been described in papers by I'm sure most of

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you are familiar with; Lynn McPherson's written books on this, and I've written much, articles and so forth -- just have not been wholly embraced. And partly is, even if we -- and I completely agree, as was said by Dr. Sandbrink, we need something, so we've relied upon these tables as this is a starting place. Don't overly rely on them, but you need something to guide you. This is the place to start, but people have not gone the next steps. And as Lynn has so forthrightly put, this is only number 3 out of 5 really critical clinical considerations, amongst others.

Something Lynn McPherson said yesterday has really stuck with me, which is, if it's too complicated, people won't do it. But that is just a reality that I think we have to live with and acknowledge. So how do we now pragmatically deal with the fact that it is very complicated and people won't do the right thing? If they did, we wouldn't have necessarily had all the problems we've had in the last ten years or so, or more.

So to answer these questions with all that

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as pretext, the notion of a gold standard -- well, morphine has been around for a long time, so it is a gold standard against which everything else is compared. It's just become a de facto default, whereas we know that, sadly, morphine is a useful drug, but it's also a very dirty drug with M3 and M16 metabolite , and other disposition problems with histamine release. It's versatile in certain ways, but it certainly has its limitations.

So it's just odd that that's become the gold standard, though it's a really historic one, but doesn't necessarily make pharmacological or clinical sense. Maybe there is no gold standard per se, but what we do is simply have to have a relative -- as we talk about relative potency -- and relative experimentally based conversions where we don't have good data. Because let's face it; almost all the drugs we've been talking about have not been directly compared in multidose, crossover studies, with no less different formulations of morphine to these other drugs. So it's quite specious to use this as a

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gold standard.

The second point, then, is really an introduction to a whole new idea. I brought this up yesterday, I guess prematurely, but I was really trying to maybe get some thoughts about this from others, but it lends itself more to discussion than it did to the clarifying questions yesterday.

That has to do with, really, recreating a whole new tool that doesn't require new science; it just requires use of skills and expertise that we currently have and applying them to this problem, this complex problem, like we have other complex problem-solving in other areas of medicine like ventilator settings in severe respiratory distress syndrome, or dosimetry in radiation therapy.

We don't just sort of scratch our heads, look at a little table, and then push a button, and then reductionistically say, okay, let's do it, and then let's add a little, subtract a little, and, oh my gosh, I forgot this variable or that variable. It's just beyond what human beings - even well-educated, well-intended health

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professionals -- can do. There's just too much variability complexity.

So I would suggest at this point that we move towards development of a more thoughtful tool, one that incorporates and demands input of variables, to the extent we have them, to get to a starting point where we start then having experimentally induced or experimentally derived conversion doses.

What I'm talking about, of course, is decision support, where instead of just looking at a tool and doing our calculations by hand, or mentally, or on paper, basically, it's a plug-and-play device. I don't want to simplify by saying it's an app, but it ultimately would become a computer-driven, decision-support tool. That's what we use in ICUs, it's what we use in radiation therapy, and what we use in a host of other domains. Why not in this area of healthcare? Thank you.

DR. STAFFA: And thank you, Dr. Fine, for bringing that up again. You'll notice I have

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flipped the question to question 5, because I think when we mentioned algorithm definitions, I think decision support can provide both qualitative or quantitative, or both, types of tools to help with this.

So again, I kind of think of questions 4 and 5 as going together. So if folks have comments on that, I would encourage you to chime in on that point, where you see the utility there, but I don't want to preclude folks from making points about question 4 as well.

Dr. Zhang, did you have your hand up? Would you like to make a comment?

DR. ZHANG: Yes. Thank you. This is Kun Zhang from CDC. First of all, I agree with what Dr. Sandbrink just commented. What I want to see is, again, a data point. I want to remind all of us, in 2019, there were about 1 million prescribers nationwide who wrote at least one opioid prescription.

The reason I say this number is I think there is a huge need for some type of tool for

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these 1 million providers. I think we need more research, understanding what is the need and what kind of tool can better help them. What we currently have, is that sufficient, or how can we improve the resources and tools provided for these large number of providers so that they can use in their clinical practice, and as a result, of course, helping patients and making sure of safe prescribing and better outcomes.

That's my comment. Thank you.

DR. STAFFA: Thank you, Dr. Zhang.

Dr. McPherson, would you like to make another comment?

DR. McPHERSON: Yes. Thank you. Lynn McPherson again. I want to get back to what Dr. Fine was just saying. I completely agree.

This is very complicated. I mean, it's not rocket science, but it's pretty darn complicated. I think we have to consider MMEs for the medical/legal opioid crisis conversation separate from the patient care conversation, and I know they certainly cross paths there. But in caring for

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patients and doing calculations and conversions, don't even bring up the MME stuff; just call it equianalgesic dosing.

But I agree with Dr. Fine. I do still think we need a super awesome equivalency chart that is constructed on the very, very best evidence we have, crossover trials, steady state that shows bidirectionality, because you can't just throw people out into the woods and expect they're going to find their way home by themselves.

But I do think, I don't know, maybe the next time I update that bloody book, I'll make it more of a critical thinking process, as Dr. Fine was just saying, where you take people by the hand and go step, by step, by step. And one of those steps is referring to the best-evidence chart; so an explicit critical thinking process.

Now, the MME thing, I think imposing these limits, it's almost become like a dirty word in a way. And yes, I do think it's had some inroads and maybe ruling out some crazy prescribing of opioids, but I don't think it's really met the mark of what

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we were hoping it would do, which is to turn around the opioid crisis. I don't think it's really done that. And I think we've seen an array of impact on patient care by imposing these MMEs.

So I think the whole MME conversation -- and as Dr. Dasgupta just pointed out, there are 47 ways to calculate the MME -- this also needs to be a critical thinking process, but a different one from the direct patient care because my patient is vomiting and he can't swallow MS Contin anymore.

So I don't think we can throw the baby out with the bathwater, but I think these are almost two separate issues, and they're two separate critical thinking processes. Thank you.

DR. STAFFA: Thank you very much for those thoughts.

Ms. Cowan, would you like to add thoughts here?

MS. COWAN: I'm sorry. Yes. I'm just trying to play around with this thing and forgot what I wanted to say.

But if we go with all of the things that

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

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

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

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pain. Thank you.

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

Dr. Comer, would you like to weigh in?

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

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

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

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

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

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

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

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

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

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

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types of firewalls connected to them, or independent grants, or no-strings-attached grants, including the risk management programs and mitigation strategies within FDA that are funded by pharmaceutical companies -- have been met not only with skepticism, but unfortunately with such levels of cynicism that they've fueled a lot of what's going on that has been very negative in terms of an impact on patients living with debilitating pain; so a lot of the comments we heard yesterday and a lot of the reminders that we've had from Penney Cowan.

Even though I appreciate the efforts of the FDA, I do recall the beginnings of this when it went from RiskMAPs to REMS, well over 10-12 years ago, and conversations that said, look, this is probably not going to go well as long as it's funded by drug companies for one reason or another, and sure enough, that's where we find ourselves. The narrative has been hijacked. Anything and everything attached to -- anything even remotely related to -- the pharmaceutical industry, can be

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construed as somehow perverted, or disingenuous, or whatever.

So with that said, if we're not going to end up with a pain institute that's publicly funded at NIH, and I still hope we will have one, I would hope that FDA would at least reconsider how to get involved in more global pain education that's more comprehensive.

It's not the FDA's job, but a lot of this is politicking. It's how to convince the insurance industry they ought to actually cover interdisciplinary comprehensive pain care; that the kinds of research that we've been talking about is actually funded; that CDC gets involved in not just naming things an opioid epidemic but actually gets to more of the main point that we have problematic opioid use, and not just because it may have been driven in certain ways by prescription opioids, but the root causes for that have not been adequately explored, and we still have not done much to improve the lives of people living with debilitating pain, so we have a pain epidemic and

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how we deal with the overlap of these things.

In discussing solutions, not only do we need a specific tool, because if we go back, again -- and I know, I'm sorry, this is a lengthy commentary here, but their history is so important. If we go back to the inception of all this, I don't remember anybody ever standing up and saying opioids are the panacea for anything and everything when a person says this hurts.

What was talked about, and educated, and taught throughout at least my entire career was, if and when such time comes when opioids may be indicated -- may be indicated -- for part and parcel of comprehensive pain treatment, we ought to know how to use that tool safely and effectively, and here's how you do it.

One tool, a tool that talks about relative analgesic equivalency and is honest about it, and says these are experimental relative potencies, or currently derived-based conversion doses, what's the tool to do it? We've talked about that as maybe decision support that can be computer driven

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and fitted on everybody's smartphone.

Yes, it is only one component, but if we talk about larger pain education to drive this forward, once again, we need a new paradigm, and one that's not necessarily attached to pharmaceutical dollars.

DR. STAFFA: Thank you, Dr. Fine. I think you've made some very good points about pain management and how opioids certainly should not be the sole focus of pain management.

I would encourage folks, as we've alluded to yesterday, the FDA developed a blueprint to provide the basis for that continuing education type training. And it's posted on our website, so folks can take a look and see. And obviously we're always interested in comments of how that could be improved, so happy to hear about that.

Dr. Chai, did you want to ask a clarifying question or make a point?

DR. CHAI: Yes. I just wanted to build upon the comments that have been made and see if we can elicit more response in that direction.

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

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

DR. STAFFA: Thank you, Dr. Chai.

I'm going to move to the next question. And

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

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

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

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

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

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

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

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

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Dr. Fine, did you want to weigh in?

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

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

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

So I'm not sure how to cross pharmacological

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classes in the same way as an interclass effort at an experimentally based conversion dose, comparing apples and apples. But I think your question, actually in a reverse way, begs should we ever be even comparing pure mu opioid agonists to more complex agonists, or partial agonists, or those drugs with certain adrenergic or NMDA-receptor actions, and is that even a manageable thing to do at this point in time for similar reasons, because the mechanisms of action are different. Thank you.

DR. STAFFA: Thank you for that comment. I think that does raise questions because, again, it gets into some of these other outcomes along with analgesia, how you convert patients or perhaps add other agents so that you're not increasing the risk of respiratory depression but perhaps increasing the analgesia, and that really depends on the indication and the type of pain you're treating, I think, as you mentioned.

I don't know if these tables really play a role there, but maybe as part of this algorithm or this broader consideration of once you go through

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and look at the table and look at what you're doing there, to be considering other drugs. I think Dr. McPherson gave some good examples of how folks often don't think about that, but that perhaps that could be built in, in terms of further research, knowledge, and understanding of how other therapies complement opioid therapy or other things to consider.

Again, but it's part of that whole education, that that calculation is just part of the entire care of the patient or, again, looking at the patient situation to determine the risk.

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

DR. COMER: Yes, just to follow up on this basic question about gaps in the science, one thing that has been really exciting in the field of treatment of opioid-use disorders have been the development of these sustained-release formulations on the order of a week or a month for reducing the illicit use of opioids.

You can imagine, actually, that some of these long lasting opioids might also have some

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applications in treating pain. I think that's something that we haven't really explored at all yet. So that's definitely a gap that we could think about, because there's sustained-release buprenorphine, for example. There are a couple of different formulations, one that's just been approved and another that's about to be approved.

DR. STAFFA: Dr. Bettinger, would you like to jump in here?

DR. BETTINGER: I didn't know if Dr. Fine had his hand raised before me. I can let him go if he --

DR. STAFFA: Okay.

Dr. Fine, did you want to make a follow-up comment, and then we'll go to Dr. Bettinger?

DR. FINE: Oh, Jeff, go ahead, please. Go ahead, please.

DR. STAFFA: We'll come back to you after, then, Dr. Fine. You'll be first up after Dr. Bettinger.

Go ahead.

DR. BETTINGER: Okay. Thank you, Dr. Fine.

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I was going to comment to Dr. Comer's original idea, which I agree with. I think it's really intriguing, even in the sense of at least it would get clinicians to think about, again, what is the goal of this MME conversion. We're not just kind of blindly following these numbers and conversion factors where we're kind of critically thinking -- going back to Dr. McPherson -- about these in those different contexts.

I also really like the idea of looking at -- as Dr. Comer said - different, long-acting, and the prospect of sustained-release opioids, especially for patients where maybe their pain is relatively managed, or they're using IR, and we know about the peaks and troughs, and they have to take it multiple times a day, and there are periods of not so great relief, looking into more extended-release opioids.

I know there have been some trials out there that have not necessarily shown significantly improved outcomes in terms of pain relative to short-acting, but I wonder if we, again, just

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continue looking at those differences; and even things like more long-acting opioids, ones like Dr. Comer was saying, the injectable buprenorphine that will last in the system for a while from a pain perspective.

I think all of those are really good ideas to look at, again, harkening all this back to the education and what does that look like in terms of educating our clinicians, who are the ones kind of left to figure this out. Is it making them all required to read Dr. McPherson short text books? Maybe that's what we need to do.

I think maybe grassroots campaigns could be an attempt to, again, have some of these conversations at the clinician level, because I think creating work groups and guidance documents are always going to be great, but I think we should be realistic. For the vast majority of all practitioners, the majority, they're going to kind of do a quick look. They're not going to really get into depth with what's going on.

I think figuring out ways we can do some

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more grassroots campaigning -- again, as Dr. Fine said -- without necessarily the involvement with pharmaceutical companies and industry, which, again, from a funding perspective, I'm not exactly sure what the answer is. But that could be another route, too. Thank you.

DR. STAFFA: Thank you, for your comment.

Dr. Fine, did you want to jump back in here?

DR. FINE: Yes. There's something that sort of was clawing at me. I took so many notes on yesterday and today that I've been digging through so I wouldn't waste all your time sifting through stuff.

One issue that we haven't really covered that I would hate to conclude today without at least thinking about a little bit, even though this is not a discussion about healthcare financing, God forbid, but it enters into everything -- one of the things that I think would be very useful for this group to at least weigh in on and at least make note of, and perhaps with a relatively large font underlined and bold is, when is it clinically

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indicated or what kind of consensus could be developed out of groupthink to do so when monitoring is a priority or is indicated in dose conversion?

Whether it's from an opioid to another opioid, or from an opioid to an non-opioid, or adding a non-opioid or vice versa, when is monitoring a critical part of clinical care rather than writing a prescription, doing a little counseling, and sending somebody home with a few notes and hoping for the best?

I suspect that if there was a guideline for that or some guidance about that, it would create great comfort for clinicians in a host of settings but also save lives.

I just want to add a clinical case in terms of that discussion that Dr. Comer brought up and I talked about, considerations where a small dose of NSAIDs, relatively speaking, or corticosteroids might substitute for a large dose of opioid. But I would also consider the circumstance where a patient almost has a significant or severe pain

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disorder that is amenable to some degree of opioid therapy but is not adequately treated, and still there's indication for either interventional or pharmacological care.

For instance, consider the circumstance of somebody with widespread metastases in the advance stages of disease, who is bedridden, can't move because of severe pain, is on a relatively high dose of opioid, corticosteroid, and NSAID, and nothing else is touching their pain; and they can't communicate, and they're becoming agitated or delirious from metabolites of whatever drugs they're on.

For instance, in my own practice, under circumstances like this, a very subanesthetic dose of ketamine, a low-dose ketamine infusion, might obviate the need for almost all opioid and allow a clear sensorium in the person actually to function, at least through the remainder of their life. But if you don't drastically reduce the opioid dose at the time of using a very small subanesthetic -- again, a dose of ketamine, like

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0.1 milligram per kilogram -- they will stop breathing because the motivation to breathe, the respiratory drive has been so much motivated by pain or by nociception.

These are complex considerations and maybe they're one-offs clinically, but unless we think about this in these kinds of comprehensive ways, when is monitoring required; how do we really accentuate safety; how we do go from one drug to another or intraclass pure opioid agonist or pure opioid agonist; how do we actually take the very limited data we have now about converting from pure agonist to, say, partial agonist like buprenorphine and do that without instigating either acute abstinence but also psychologically get people through this transition? What are the principles of practice that would support those kinds of safe transitions?

This is a larger discussion, but I thought I would at least get them onto the record. So thank you very much again. This is Perry Fine.

DR. STAFFA: Thank you, Dr. Fine.

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Dr. Comer, did you want to make a comment about this area?

DR. COMER: Yes, just a follow-up. Again, Sandy Comer from Columbia University.

Just to follow on that point that Dr. Fine was making about the risk of respiratory depression, I think another gap in the science that we have with regard to pain is how to mitigate the risk of overdose in this population.

We have good data from the field of addiction, where we know that if patients are maintained on medications, like methadone or buprenorphine -- naltrexone obviously is not a viable option here -- the risk of overdose goes down. So are there certain types of medications that would be helpful in this regard?

People who are on short-acting opioids for pain might have a higher risk, people who are on higher doses, but if they had a baseline of methadone or buprenorphine as their primary pain medication, would the risk decline, basically? That was just my suggestion for a gap.

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DR. STAFFA: Thank you. I think that's a very relevant thought.

Okay. I'm going to move to the last question. You guys have been great, but we're getting to the end of our time, and I want to make sure we have folks weigh in.

What I was hoping is that if you've had a chance to think about all this -- and we've talked about a lot of different areas -- I think we have a lot of things to go back and discuss about forming perhaps a working group around this, different topics for research agenda, and that's going to be really helpful to us.

But I'd like to ask if everybody on the panel could weigh in and at least let us know -- and again, the folks outside of FDA because this is our unique chance to hear from you -- if you had to pick one thing that you thought was the most important thing for us to focus on or prioritize in terms of a gap, whether it's an area of research or the education, what one thing do you think is the most important thing for us to start

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with or what group of things? But you can't take everything as a group of things. I'm not going to let you do that.

It will help us really make sure that we put our efforts in the direction that folks think are really the most important at this point in time. We are very committed, this working group at FDA and with our federal partners, for trying to improve the science in this area, so we'd love to hear what your thoughts are.

Dr. Fine, you seem to be the brave one that wants to go first. Go for it.

DR. FINE: I've lost all pride in my old age; the years have grounded me down. The priority I would like to see would be a decision-support smart tool that guides critical thinking for purposes of safety, as well as efficacy, when it is determined that opioids are indicated or continue to be indicated.

DR. STAFFA: And I'm assuming that's a tool that's been developed and validated, so it has good science behind it, right?

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

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

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

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

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any way to improve the situation that you described?

DR. DASGUPTA: Yes. I think on a practical level, there are a lot of software vendors, and whether this is something baked into Epic or on a PDMP dashboard, or something that's even like an in-clinic based tool, I think the definitions really have to be standard if we're going to continue to use them.

As much as I'd like to say more money for basic theory research, what I think actually is needed right now is harmonization. A lot of times those software vendors write out how they're calculating these things in code, and then that code becomes proprietary, so having a common code base that's available across different platforms.

There are a lot of logistical things we can do, so at least get to standardized and to bake in some of the broader clinical decisions and not just rely on the number.

DR. STAFFA: Thank you. Thank you very much for your efforts in that space.

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Dr. Zhang?

DR. ZHANG: Thank you. This is Kun Zhang from CDC.

Dr. Staffa, I want to add a point you made, which is education. If you asked me to choose, I would emphasize that, education for those providers and patients. As I mentioned, as of 2019, there were about 1 million prescribers of opioids. So that's my comment.

DR. STAFFA: Thank you. Thank you for weighing in.

Dr. Sandbrink, I think you're the sole survivor of our VA participants. Any comments or prioritizations here?

DR. SANDBRINK: Yes. Friedhelm Sandbrink, Veterans Administration, Washington, D.C.

Thank you. I really feel that rather than me commenting right now on research, I feel the immediate need is in many ways educating the community, and that probably means also the legislators, about the limitations of what we have been doing in regard to MMEs.

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I think we really have to step back and say, yes, research is needed in regard to specifically what is the appropriate application of MME levels and the specifics that we all discussed already, but we also, I think, need to clarify at this point what are the limitations. I think people across the board need to be educated about that in many ways so that this currently ongoing misinterpretation or misperception is being addressed. So maybe that's just an encouragement in that regard.

I really feel like it's very hard to develop these decision-support tools. We are trying to do it in the Veterans Health Administration and among others, that takes not only the medication factors into account, but then even more complicated is the patient factors because the risks and the benefits depend obviously on the prescription, on the medication, on the drug, on the formulation, how it's being administered; but just as much, or probably more, at least in regard to long-term risk, on the patient characteristics.

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So we have our decision-support tool that we provide to our providers, at least in regard to risk assessment; our certification tool for opioid risk mitigation that allows an assessment using predictive analytics in regard to an assessment of risks, including for patients who are maybe not on medication yet but are being considered for opioid medication and takes the MME levels into account and that has three tiers in that regard.

So we are on the way, but we also realize that the patient factors are so very much important, and I think we should never forget that. Thank you.

DR. STAFFA: Thank you so much for pointing that out.

Dr. Chidgey, did you have another comment?

(No response.)

DR. STAFFA: Dr. Chidgey, your hand is not raised, but did you have another comment? I thought I saw your hand up.

DR. CHIDGEY: I forgot to take it off. I apologize.

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

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

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

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

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something that comes out of this -- how can the FDA really push back against this narrative, that is a very dangerous and propagandic narrative, that supports an agenda but doesn't really speak to the health concerns of people living with debilitating pain, and the practitioners, and the healthcare professionals that are there who would advocate and want them to live as healthy lives as they can; all the different areas of expertise that are involved as represented on this call. Thank you.

DR. STAFFA: Thank you for your comment.

Dr. Sandbrink, did you have a final comment on our prioritization question? Go ahead.

DR. SANDBRINK: Yes, just actually two thoughts or two comments. Friedhelm Sandbrink, Veterans Health Administration, VA.

First of all, in regard to the role of the pharmacists, we in the Veterans Health Administration have used pharmacists greatly, obviously recognizing expertise, but in addition, using them also as providers and supporting care administration and care delivery.

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What we notice is there are clearly these differences between states. I think some kind of effort to try to standardize the role of the pharmacists, including where they have prescribing authority and others, may really help us all to make better use of these great medical providers with the expertise that they have.

The second one that I just wanted to mention is specifically in regard to buprenorphine for pain management. There's really a lack of, I think, understanding or really a need in regard to more education, and possibly a research need, to try to understand this better.

There's a lot of information available about buprenorphine. Much of it is related to, obviously, using it as medication for OUD treatment. But I think specifically for pain management and what is the analgesic potential of that medication, and how to make best use of this, especially in regard to medication conversions in regard to analgesia, I think there's a lot of need. Thank you.

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DR. STAFFA: Thank you so much.

Well, I want to thank everybody for a very, very full discussion. I know we asked for a lot, but we got a lot of great thoughts. We have a lot to bring back to the ranch for some great discussions and some ideas for how to continue the momentum. I can promise you that we are committed to follow this through and to see where this takes us, so we can improve the science in this area.

With that, I'm going to turn it back over to Dr. Chai, who will be, I think, closing our meeting. Thank you.

Closing Comments – Grace Chai

DR. CHAI: Thank you, Dr. Staffa.

I hope I speak for many others that this was really such a fantastic workshop for me. I believe that we've achieved our main goal for this meeting, which is collectively, for many of us -- and I hope we've all learned something new -- more on the science underlying the space, which we are referring to as morphine milligram equivalents or MME.

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As you can hear, it's much broader than what we may have initially come in with. I stated earlier, the allure of MMEs is in its simplicity, but as demonstrated by all the presentations and discussions that we've had, it's anything but. This is hard and challenging, but as reinforced by all the patient voices we've heard, as well as comments to the public docket, it is critical for us to keep leaning in when it is hard and together push forward to advance the science in this space.

For the patients and public health, we need to better equip all stakeholders with the tools and with a better more thorough understanding of the science and advance in the gaps when we don't have enough information.

I truly hope you've enjoyed the presentations as much as I have. We will be posting meeting slides and recordings in a few weeks, with the transcript to follow at a later date, closer to August. As you can see, this was a tremendous amount of discussion, so that transcript will be available later.

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

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

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

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

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

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

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

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

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

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