

Morphine Milligram Equivalents (MMEs)

Current Applications and Knowledge Gaps, Research Opportunities, and Future
Directions

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What is an MME?

- Definition: The amount of milligrams of morphine an opioid dose is equal to when prescribed. Calculating MME accounts for differences in opioid drug type and strength.^a

MMEs are increasingly being used to indicate abuse and overdose potential and to set thresholds for prescribing and dispensing of opioid analgesics.

Purpose

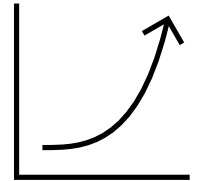
- To bring stakeholders together to discuss the scientific basis of morphine milligram equivalents (MMEs), which are widely used as metrics in multiple areas throughout the healthcare system

Goals

- Describe the science underlying MMEs
- Describe uncertainties and complexities in calculating/applying MMEs as:
 - **Opioid Conversion Factors**
 - **Risk predictors for overdose/nonmedical use/opioid use disorder**
- Discuss a research agenda to fill knowledge gaps to refine and improve the use of MMEs across applications

Scientific Workshop

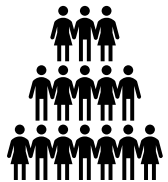
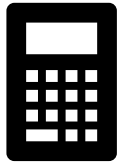
- Patients and Public Health
 - The expanded and varied uses of MMEs and the impact on patients reinforce the need to understand and build the science of MMEs
- Focus is on describing and enhancing the science
 - Discussion of specific regulatory actions, policies, and applications of MMEs is not the focus of this meeting
 - Our goal is to facilitate a productive discussion to better understand and advance the science



Opioid Conversion Factors



- Based on small clinical studies in limited populations
 - Clinical Practice: Originally intended to assist clinicians in determining initial dose when converting an individual patient's opioid therapy
- Resources (e.g., tables, online calculators) contain different conversion factors
- Patient and drug characteristics
 - Ex. Opioid tolerance, pharmacogenetics
 - Ex. Partial agonists (buprenorphine), novel drugs (tapentadol)



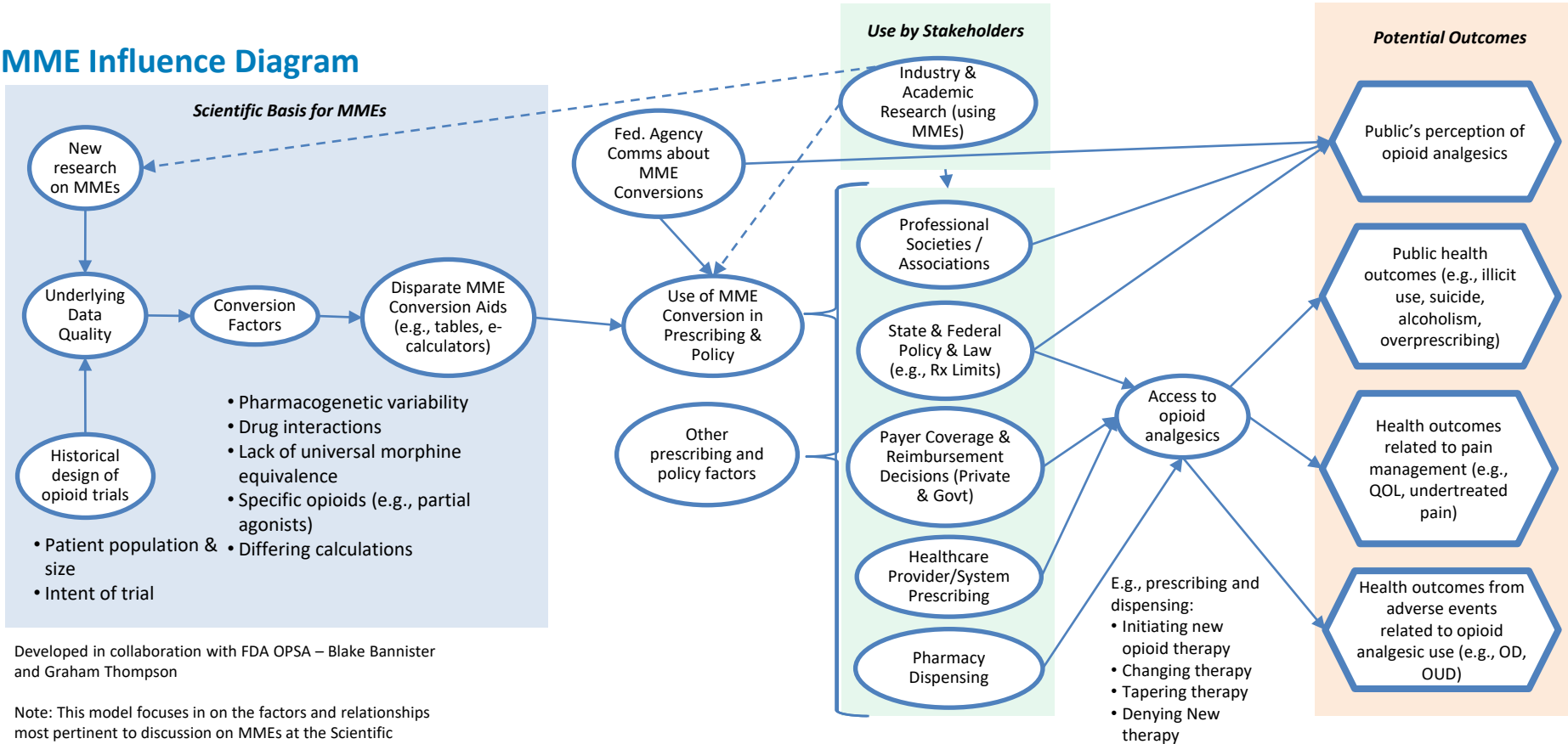
MMEs and Risk

- Epidemiologic studies show convincing association between increasing daily dose of opioid analgesics and increasing risk of ***overdose***
 - Studies have generally used daily MME threshold categories to assess risk (e.g., > 50 MME/day, > 90 MME/day)¹ but stated no clear threshold
- Studies have also examined the association between daily dose and adverse outcomes (e.g., opioid use disorder/addiction, misuse/abuse), but causality is unclear

¹ Bohnert et al. Med Care 2016; 54(5):435-441

Expanding Scope of Influence

MME Influence Diagram



Developed in collaboration with FDA OPSA – Blake Bannister and Graham Thompson

Note: This model focuses in on the factors and relationships most pertinent to discussion on MMEs at the Scientific Workshop. It does not capture every factor or relationship associated with MMEs.

Conclusion

- **Given the expanded and varied uses of MMEs, understanding and building upon the science of MMEs is needed to refine and improve the scientific basis for MME applications**
 - Scientific Workshop goals are to understand and seek to improve the scientific basis of MMEs
 - Inform a future research agenda

Meeting Materials

- Available Online
 - Meeting agenda
 - Speaker bios and disclosures
 - Panel discussion questions

Agenda: Day 1



- **Impact of Science on Real Life Experiences:** Penney Cowan
- **Overview of Current Applications and Uses of MMEs:** Corinne Woods
- **Calculating Conversations in Opioid Conversions:** Mary Lynn McPherson
- **Individual Patient & Medication Factors that Invalidate Morphine Milligram Equivalents:** Jeffrey Fudin
- **Opioid Prescribing and the Opioid Safety Initiative in the Veterans Health Administration:** Friedhelm Sandbrink, Thomas Emmendorfer, Fran Cunningham
- **Clarifying Questions**

Lunch

- **Overview of the Opioid NDC and MME Analytical File Compiled by CDC:** Kun Zhang
- **MHRA-UK work in development of MME tables:** Justin Pittaway-Hay
- **Improving information for opioids prescribers on the safest possible effective dose of morphine or equivalent: a UK perspective:** Maria Luisa Molinari
- **Clarifying Questions**
- **Public Comment Session**

Agenda: Day 2

- **Welcome and Recap of Day 1:** Grace Chai
- **Opioid Conversion Information in Approved Labeling:** Mary Therese O'Donnell
- **Nonclinical Pharmacology and Toxicology Considerations Regarding Opioid Comparisons and Risk Assessments (Basic Opioid Pharmacology 101):** Dan Mellon and Donna Volpe
- **MME calculations and Abuse liability considerations:** Chad Reissig
- **Clarifying Questions**
- **Relative potency of oral and intravenous oxymorphone compared to other μ opioid agonists in humans:** Shanna Babalonis
- **Opioid Potency: Pharmacological and Nonpharmacological Factors:** Sandra Comer
- **Inches, Centimeters, and Yards: Overlooked Definition Choices Inhibit Interpretation of Morphine Equivalence:** Nabarun Dasgupta
- **Clarifying Questions**

Lunch

- **Panel Discussions** (FDA Co-Moderators: Judy Staffa and Jennifer Nadel)

Panel Discussion Questions

- 1) Discuss any potential knowledge gaps in the science underlying MMEs across various applications.
 - a. Drug Considerations
 - b. Patient-Level
 - i. analgesia/opioid rotation/conversion
 - ii. risk predictor
 - iii. other
 - c. Population-Level/Public Health
 - i. risk predictor
 - ii. research
 - iii. other
- 2) Discuss types of studies and designs that may be helpful to address knowledge gaps in the science across various applications.
- 3) Discuss additional factors that should be considered to inform/supplement the use of MMEs, at a patient-level and/or population-level across the various applications.

Panel Discussion Questions (cont'd)



- 4) Given the availability and variability of multiple MME conversion tables, analytical files, online calculators, references, and tools, discuss the benefits and limitations of a common MME reference table(s) (gold-standard) vs. multiple reference tables.
 - a. Discuss if a gold-standard reference table(s) is necessary
 - b. Discuss for what purpose(s) is it possible/feasible
- 5) Discuss calculation of MMEs (MME per day, etc.).
 - a. What are the challenges and knowledge gaps in the calculation of MMEs for patient care decisions?
 - b. Discuss whether different MME conversion factors or algorithm definitions are needed for certain patient populations (e.g., opioid-naïve patients, patients with current opioid use), for use at the patient-level or aggregate/population level.
- 6) What are other gaps in the science that haven't been discussed; where and how can research enhance/refine/develop knowledge about MMEs to support the varying applications and uses?
 - a. How should novel opioids and/or analgesics be considered in this paradigm?
- 7) Based on previous discussions, prioritize the research to fill the identified gaps.